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INTRODUCTION TO THE THIRD REPORT OF THE ROBERT M. THOMPSON PELLAGRA COMMISSION OF THE NEW YORK POST-GRADUATE MEDICAL SCHOOL AND HOSPITAL*

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The pellagra commission of the New York Post-Graduate Medical School began its studies of pellagra in the spring of 1912 and the laboratory and field investigations were continued until the fall of 1914. A brief supplementary field study was conducted in August, 1915. During 1912 and 1913 the work of the commission was supported by a fund donated jointly by Col. Robert M. Thompson and Mr. J. H. McFadden. Since the end of 1913 funds for the continuance of the work have been provided by Col. Robert M. Thompson and Dr. Geo. N. Miller. The personnel of the commission proper has continued to be the same from the beginning. Dr. J. F. Siler, Capt. Med. Corps, U. S. Army, has been detailed to this work continuously, except for brief interruptions of a month or six weeks' duration, from the spring of 1912 to the last of July, 1915. Dr. P. E. Garrison, Passed Asst. Surg., U. S. Navy, was detailed to the investigation continuously from the spring of 1912 to November, 1913. He was detailed elsewhere from December, 1913, to June, 1914, and after working on pellagra during the summer of 1914, he was compelled to give up further participation in the work by a call to active sea duty. Dr. W. J. MacNeal, the civilian member of the commission, has continued since the spring of 1912 to devote part of his time to the work of this commission, although by far the major portion of his time each year has of necessity been given to other work in the laboratories of the New York Post-Graduate Medical School.

* Submitted for publication March 9, 1916.

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This pellagra commission has issued two series of papers, the first series[1] dealing with certain phases of the work up to the end of 1912 and the second series[2] dealing with the investigations up to the end of 1913. The results and the conclusions of this earlier work have been confirmed and amplified by the subsequent investigations. Some of the results are merely confirmatory of facts already well known concerning pellagra; others are somewhat at variance with previously recognized conceptions and old theories of the etiology of pellagra, including the ancient theory of dietary deficiency, again exploited by Sandwith[3] and others in the recent literature. It is our purpose to present in this third report those portions of our recorded observations which seem to have the most important bearing upon the unsettled problems of pellagra.

Inasmuch as the various members of the commission have been taken away from the work, it seems very probable that the present series of papers will represent the final report to be made by the commission as originally constituted. It is hoped, however, that the inves-

1. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Pellagra—A Summary of the First Progress Report of the Thompson-McFadden Pellagra Commission, Jour. Am. Med. Assn., Jan. 3, 1914, lxii, 8; Siler, J. F., and Garrison, P. E.: An Intensive Study of the Epidemiology of Pellagra: Report of Progress, Am. Jour. Med. Sc., 1913, cxlvi, 42, 238; Jennings, A. H., and King, W. V.: An Intensive Study of Insects as a Possible Etiologic Factor in Pellagra, Ibid., 1913, cxlvi, 411; Myers, V. C., and Fine, M. S.: Metabolism in Pellagra, Ibid., 1913, cxlv, 705; Hillman, O. S.: Some Hematological Findings in Pellagra Ibid., 1913, cxlv, 507; MacNeal, W. J.: Observations on the Intestinal Bacteria in Pellagra, Ibid., 1913, cxlv, 801. This entire series of papers, together with a Table of Contents, is included in Pellagra—First Progress Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate Medical School and Hospital, New York, 1914, pp. iv + 148.

2. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Further Studies of the Thompson-McFadden Pellagra Commission—A Summary of the Second Progress Report, Jour. Am. Med. Assn., 1914, lxiii, 1090; Introduction to the Second Progress Report of the Thompson-McFadden Pellagra Commission, Arch. Int. Med., 1914, xiv, 289; A Statistical Study of the Relation of Pellagra to Use of Certain Foods and to Location of Domicile in Six Selected Industrial Communities, Ibid., 1914, xiv, 292; The Relation of Methods of Disposal of Sewage to the Spread of Pellagra, Ibid., 1914, xiv, 453; Hillman, Oliver S., and Schule, Paul A.: Further Observations on the Blood Count in Pellagra, Ibid., 1915, xv, 147; Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Statistics of Pellagra in Spartanburg County, S. C., Including Geographical Distribution of the Disease and Its Relation to Race, Age, Sex and Occupation, Ibid., 1915, xv, 98; Singer, H. Douglas: Mental and Nervous Disorders Associated with Pellagra, Ibid., 1915, xv, 121. This entire series of papers, together with a Table of Contents, is included in Pellagra II—Second Progress Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate Medical School and Hospital, New York, 1915, pp. iv + 169.

3. Sandwith, F. M.: Can Pellagra Be a Disease Due to Deficiency in Nutrition? Tr. Nat. Assn. for Study of Pellagra, 1912, ii, 97; Is Pellagra a Disease Due to Deficiency of Nutrition? Tr. Soc. Trop. Med. and Hyg., 1913, vi, 143.

tigation of pellagra thus begun under the auspices of the New York Post-Graduate Medical School and Hospital will be continued under the same or under other auspices until the numerous theories concerning the nature of this disease shall have been completely overshadowed by scientifically demonstrated facts.

The series of papers, constituting the third report, includes the important contributions of some of those scientists who have collaborated with our commission by undertaking the study of pellagra from particular individual points of view. We consider ourselves especially fortunate to have had the collaboration of these investigators and are very grateful to them for the papers which they have written for this report. Needless to say, these collaborators are alone responsible for their interpretations and conclusions, and they alone deserve the credit for the results which they report. It is a special pleasure to acknowledge our obligation to Dr. C. B. Davenport, to Dr. Elizabeth Muncey and to Dr. E. B. Vedder, Capt. Med. Corps, U. S. A., for their studies of heredity and dietary deficiency in pellagra. We wish also to give credit for faithful technical assistance to Dr. F. L. Letts and to Mr. Sam Goldin.

THE HEREDITARY FACTOR IN PELLAGRA*

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I. STATEMENT OF THE PROBLEM

In certain parts of our country, and above all in our southern states, there are occasionally seen persons whose hands, feet and even other parts of the body show chronic, symmetrically placed,[1] eczema-like rough patches or a formation of bullae and desquamation over larger or smaller areas. A condition of dermatitis may be due to a number of causes; to tuberculosis, to a filamentous fungus, to poisoning from without or within. Particularly the poison that can be expressed from certain mucors will, when injected into the veins of a rabbit, cause extensive desquamation of a similar sort. But in certain of these persons there is, in addition to the chronic desquamation, a persistent diarrhea or dysentery.[2] In consequence of a disturbing factor, probably a tissue poison, of whose presence these are merely indications, the affected person is liable to die; or else he recovers as the cooler weather comes on, to relapse into the same condition the following spring; or perhaps he recovers permanently. Now, these two states, skin inflammation and diarrhea, may occur independently of each other, but when they occur together the diagnosis of pellagra is nowadays rendered. If in addition to these two symptoms an individual shows an unwonted nervous or mental state, whether unusually excited or unusually depressed or confused and demented, then the diagnosis of pellagra is given with greater confidence.

Now, is this association of traits a necessary one, due to a single cause, for example, the introduction of a specific poison of parasitic or other origin, or is it an accidental association; just as one will find blondness, hair curliness and short stature combined in a certain proportion of the population? If an anthropologist should describe this type and give it a name, then observers would easily detect persons belonging to this type and the type would then begin to exist.

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* From the Eugenic Record Office, at Cold Spring Harbor, Long Island, N. Y. This paper forms a part of the third report of the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

1. "Symmetry of dermal lesions is a widespread phenomenon. Thus in leprosy the eruption is frequently symmetrical, remarkably so, but this is by no means a constant feature."—Cantlie, J.: Allchin's Manual of Medicine, I, p. 239.

2. Persistent diarrhea accompanies skin diseases of other types. This is so in leprosy.

It would not have existed before because there cannot be a type without a definition and a name. I do not wish to assume the rôle of an iconoclast, yet I cannot but be impressed by the difficulties that are met with in the diagnosis of pellagra. These difficulties led Lavinder[3] to say: "It is possible, of course, but rather unlikely, that more than one morbid entity may at present be included under pellagra." And the same author tells of a French school which speaks of the pellagrous syndrome. Also Lombroso said: "There is no disease; only the diseased." It is generally held that the erythema or dermatitis is the essential characteristic of the disease. But some Italian authors speak of pellagra sine pellagra, meaning that skin lesions are absent. The nervous and mental symptoms are not found in most cases. "In Italy it has been variously estimated that from 4 to 10 per cent. of pellagrins are insane."[3] Grimm[4] states that "In this country about 7 per cent. of the pellagrous whites are insane." And Singer[5] finds that, in 1912, 6.2 per 10,000 pellagrins from Spartanburg County were committed as insane.

II. Hypothesis

To make progress in the inquiry concerning a possible hereditary factor in so ill-defined and variable a disease as pellagra, it is first of all necessary to select some hypothesis, based upon the best available knowledge, to see if it will work. Preliminary studies show at once that pellagra is not inherited like eye color; if there is any factor of heredity at all it must be largely obscured by numerous other factors.

To the best of our knowledge, pellagra is the reaction of the individual to the poisons elaborated in the body, probably by a parasitic organism. This accords with the conclusion of Siler, Garrison and MacNeal,[6] that pellagra is in all probability a specific infectious disease communicable from person to person. These poisons cause, or tend to cause, inflammations and frequently tissue necrosis in the highly vascular layers that lie below epithelial surfaces, such as the skin, the

3. Lavinder, C. H.: Pellagra, A. Précis, Pub. Health Bull., 1912, No. 48, Ed. 2, pp. 29, 30.

4. Grimm, R. M.: Pellagra: A Report on Its Epidemiology, Pub. Health Rep., March, 1913, No. 120, pp. 5, 8.

5. Singer, H. D.: Mental and Nervous Disorders Associated with Pellagra. The Archives Int. Med., xv, 121, 149.

6. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Pellagra: A Summary of the First Progress Report of the Thompson-McFadden Pellagra Commission, Jour. Am. Med. Assn., 1914, lxii, 8; Introduction to the Second Progress Report of the Thompson-McFadden Pellagra Commission, The Archives Int. Med., 1914, xiv, 289; Further Studies of the Thompson-McFadden Pellagra Commission; a Summary of the Second Progress Report, Jour. Am. Med. Assn., 1914, lxiii, 1090.

lining of the mouth, stomach and intestine. The inflammations are most destructive in individuals that are least fitted to resist their untoward effects or provide a self-regulation. It is probable that the inflammation of the skin, lining of the mouth and various portions of the gut are incited by the same irritant; for such an association is found in some other diseases, for example, leprosy. Thus the external and the internal inflammations may be regarded as fundamentally one and the same symptom.

Further, in persons so disposed, the toxin of the disease may disturb the harmonious adjustment and coordinate working of the elements of the central nervous system, resulting, in different individuals or at different times, in underinhibition or overinhibition, in mental confusion, disorientation and other symptoms. Nervous and mental troubles are found in other diseases in which dermatitis is a symptom, for example, in leprosy, in which neuritis, and eventually neuralgia, are usual; also, in typhoid fever depression and confusion are common.

The nervous changes in pellagrins have been studied by Dunlap,[7] who finds in the motor areas of the brain a swelling of the nerve cells and a heavy pigmentation. These changes are identical with those described under the term "central neuritis;" they are found also in cases of Korsakoff syndrome, and in chronic alcoholism. A similar swelling of nerve cells has been seen in the spinal cord in cases of beriberi. There is, therefore, no specific nervous change characteristic of pellagra, but only a change which it shares with other conditions of nerve irritation, in some cases, as in alcoholism, clearly associated with poisoning.

As this paper was about to be sent to the printer there came to my hand the second report of the pellagra commission, containing Singer's paper. Singer concludes that "pellagra is especially frequent in individuals of faulty nervous organization and in consequence there occurs, in association with it, a greater percentage of such disorders as dementia praecox, manic-depressive insanity, hysteria, etc., than prevails among healthy persons, yet the vast majority of the mental disturbances occurring in connection with pellagra are of no more significance *qua* 'insanity' than are the deliriums of typhoid fever." That there should be a correlation between mental insufficiency and pellagra is not strange, since the mentally insufficient are, on the whole, less likely to appreciate the importance of sanitary surroundings and less able to avail themselves of them, and the reports of the pellagra commission prove the close relation of pellagra to poor sanitation. No doubt, also, persons who are mentally well developed are, on the whole, more likely to care for their bodies and keep themselves in good condition than are

7. Dunlap, Charles B.: The Pathological Changes in the Nervous System in Pellagra, New York State Bull., February, 1915.

the mentally deficient or unstable. Other things being equal, pellagra is more liable to make headway in "Nam Hollow"[8] than in the cottages on the cliffs at Newport.

Our hypothesis is that in the pellagra reaction there is a hereditary factor. This hypothesis is supported by certain general and by certain specific considerations. Generally, we may say that any disease, simple or compound, is known by its symptoms. Now symptoms of disease are the behavior or reaction of the organism, its organs and tissues, to the presence of certain specific stimuli or irritants that are abnormal to the body. What the reaction shall be depends not only upon the nature of the specific stimulant, but also upon the specific nature of the reacting organism or part. And if there is one thing of which experience perfectly assures us it is that different individuals react dissimilarly to the same stimulus. Such dissimilarity of reaction is conditioned both by fundamental dissimilarity in the constitution of the organism and by dissimilarity in antecedent experiences of the organism; but the latter, in turn, is conditioned in part by the former; so that the fundamental dissimilarity of the constitution of the organism must be held to be the principal cause of the diversity which persons show in their reaction to the same disease-inciting factors.

This constitution of the organism is a racial, that is, hereditary, factor. And if it appears that certain races or blood lines react in the pellagra families in a specific and differential fashion, that will go far to prove the presence of a hereditary factor in pellagra. A superficial consideration of the epidemiology of pellagra suggests that colored persons, who differ from most white people in having more or less negro blood, are less subject on the whole to the disease than white persons. Thus Siler and Garrison[9] in their early studies found pellagra nearly five times as prevalent among all white people as among negroes, or, exclusive of the cotton mill villages, two and one-half times as prevalent among the white population as among negroes. If the sanitary conditions of the white people were much inferior to those of the negroes the difference of incidence might be explained as due to such conditions, but this seems not to be the case. Siler and Garrison state that on inquiring of physicians, "without exception we were informed that pellagra in negroes was of comparatively infrequent occurrence." In the same tenor Grimm[4] states: "In the districts which I visited pellagra seemed to spare the negro to a remarkable extent, and it was not unusual to find a physician who, although he had seen many cases of

8. Eugenics Record Office, Memoir No. 2.

9. Siler, J. F., and Garrison, P. E.: An Intensive Study of the Epidemiology of Pellagra; Report of Progress, Am. Jour. Med. Sc., 1913, cxlvi, 42, 238; also reprinted in Pellagra: First Progress Report of the Thompson-McFadden Pellagra Commission of the New York Post-Graduate School and Hospital.

pellagra among the whites, had never seen one among the blacks." But the proportion of pellagrins who die or go insane is stated by him to be larger among the negroes than among the white population. We have thus here apparently strong evidence of a racial difference, and that is synonymous with a hereditary difference. However, in 1915, Siler, Garrison and MacNeal,[10] while confirming their earlier statistics that for Spartanburg County "the disease was about three times more prevalent in the white population as a whole than in the negroes," conclude, "we are inclined to believe that negroes as a race are only slightly, if at all, less susceptible to pellagra than the white population."

In view of the dependence of pellagra on industrial conditions and sanitation and the difference in these respects between the white and the negro population in different counties and states; and in view of the fact that all grades of hybrids between white and negro are grouped as colored, or negro, it is difficult to draw correct inferences as to susceptibility from the apparent difference in morbidity between the negro and the white population.

A consideration of the question whether even inside of the group of white persons hereditary strains differing in their reaction to the cause of pellagra are to be found must be deferred until we have further analyzed the nature of pellagra. The considerations already presented justify, I think, the hypothesis that there is in pellagra a hereditary factor.

To summarize: "Pellagra" is a term applied to inflammations and ulcerations of the musculovascular layer of the skin and intestine, doubtless due to the presence of a toxic agent which also induces in predisposed persons nervous and mental disturbances. The differences in the degree of expression of these symptoms are due, among other things, to differences in the hereditary constitution of the affected individuals, and variation in the symptom complex is due to variations in the constitutional, or hereditary, susceptibility or resistance of the different organs affected by the toxin.

III. Test of the Hypothesis

In the first report of the Thompson-McFadden Pellagra Commission[6] there were found for the different townships of Spartanburg County, population 83,000, proportions of pellagrins varying from 0 to 71 per 10,000. In the city of Spartanburg, with a population of 17,500, eighty-five cases were described, or forty-nine per 10,000, or less than

10. Siler, J. F., Garrison, P. E., and MacNeal, W. J.: Statistics of Pellagra in Spartanburg County, S. C., including Geographical Distribution of the Disease and Its Relation to Race, Age, Sex and Occupation, The Archives Int. Med., 1915, xv, 98.

one-half of 1 per cent. If now in many families more than one case is found in a family of under twenty-five or even fifty persons, the chances are large that the association is not an accidental one. As a matter of fact, out of 142 families reported on by Dr. Muncey, thirty-seven, or nearly one fourth had more than one case of pellagra. Actually, families with five cases are not uncommon, being nine out of thirty-seven, and even families with eight and nine to the family of close blood relations are known. This high incidence of pellagrous symptoms among blood relatives may be due to contamination through association, or it may be due to constitutional similarity, such that when one member of a family is liable to the disease others are liable also. I think the evidence shows that both possibilities are realized. The evidence for contamination is strong, but the evidence for constitutional diversity is not less strong.

1. EVIDENCE FOR THE COMMUNICABILITY OF PELLAGRA

That infection plays a rôle in the spread of pellagra can, I think, hardly be doubted. The case of mating A (Fig. 15), is especially suggestive. At a time when pellagra was almost unknown in Spartanburg County, a married woman was associated in her work with Italian immigrants during one summer. The next spring she had the typical symptoms of pellagra and died of pellagra in a few months. This was in 1894. In 1899 the mother of this woman first showed signs of pellagra; she lingered along, showing marked mental symptoms, until 1903. Her husband, father of the propositus, revealed symptoms of pellagra the year his wife died; he failed mentally and died in 1910. Meanwhile, one of his older daughters was stricken with the disease in a severe form, was nursed by various friends and neighbors, and finally died in 1910; and many new cases of pellagra broke out in the mill village the next year. A 5-year-old daughter of the last-named victim died from pellagra the same year (1910) as her mother, and the next year another daughter was stricken, but still resists death. Certainly this looks like communication.

Other cases of possible communication were collected by Dr. Muncey. Thus, in the progeny of mating C (Fig. 38), a girl first showed the disease in the spring of 1908 and it affected especially the skin of the feet and legs. Her father dressed her desquamating and raw skin and he came down with the disease in the spring of 1909 and died of it in June, 1910. Again, in mating 10 B, we have the history of a father in whom pellagra appeared in 1911 with severe dermal symptoms and these have recurred every spring since. His ten-year-old son sleeps with him, and in July, 1914, he developed severe erythema with slight intestinal disturbance.

Again, mothers are more intimately associated with children than are fathers. Correspondingly, we find 57 cases of mother and child, both pellagrous, and only 17 of father and child. But mothers are 2.3 times as apt to be pellagrous as fathers. Multiplying 17 by 2.3 we get 39, the theoretical number of children to contrast with the 57 pellagrous children of affected mothers. And the difference between these two numbers roughly corresponds with that of paternal and maternal contact. This, again, speaks for communication.

An examination of the pedigrees shows a large number of cases in which both parents are affected, and one seems to have become infected by the other. I give some cases:

Case C (Fig. 12).—The father of a family which lived next door to a pellagrin developed a well-marked case of pellagra in April, 1911; a son showed the same symptoms in the same month and the mother in June of the same year.

Case B (Fig. 11).—Father and mother showed the disease at about the same date.

Case B (Fig. 9).—The father died of pellagra in 1909; the mother came down with it in June, 1912.

Case C (Fig. 35).—The mother had typhoid fever in 1892 and dysentery for several years following in the summer. In May, 1912, typical symptoms of pellagra appeared, and in the same month they appeared in her husband, who was tubercular and very weak.

Case A (Fig. 15).—This is the case of a man and wife whose daughter worked with Italians and contracted the disease in 1894. The mother first showed pellagra in 1899; she died of it in 1903 and her husband contracted pellagra in the same year, dying of it in 1910. A daughter of this pair died in 1910 of pellagra and her husband not long after had typhoid, followed by eczema.

Of the following cases no figures were made for this paper. The references at the end are to the families fully described in the paper of Dr. Muncey, which follows this:

Case A, C.—A man living in the endemic area developed pellagra in the spring of 1909 and died of it in August. His wife, who cared for him until he went to the hospital, had an attack the next spring, and this recurred (S. B. family).

Case B, B.—A man developed pellagra in 1911 and this has recurred each spring since. His wife had a severe attack in 1914 (T. family).

Case C, B.—A widower showed pellagrous symptoms in 1909 and was nursed by his daughter; she had good health until pellagra set in in 1911, and her husband developed the disease in 1912 (B. S. family).

Case D, B.—A woman had a severe attack of pellagra in the autumn of 1909 and died of it in April, 1910. Her husband had pellagrous symptoms in 1910 and these have recurred annually since (S. family).

Case E, A.—A housewife developed pellagra in May or June, 1911, and died of it in November, 1912. Her husband, generally of good health, developed typical symptoms of pellagra in November, 1912, and these recurred in 1913 (B. R. family).

Thus, in a marked proportion of matings husband and wife developed the disease in such time relations as to make it probable that the

disease was communicated from one to the other. In these cases there was no close blood relationship between the consorts. The cumulative evidence of communication seems irresistible, and such communication may be readily admitted.

2. EVIDENCE OF CONSTITUTIONAL SUSCEPTIBILITY TO PELLAGRA

The fact that pellagara is communicable does not, however, render the existence of a hereditary factor less probable. For it is not the parasite that causes the disease; the symptoms of the disease are the way the organism reacts to the parasite and it is clear that the organism has as much to do with this result as the parasite. And just as we find certain children who are exposed catching the disease, so we find others, equally exposed, going scot free. Thus from mating F, B are derived four children of whom three came down with pellagra, but the fourth, living in the same house as the others, has not had it. Again, from mating C (Fig. 12) came four children, of whom three were attacked, while one, the oldest girl, has never shown any symptoms of pellagra. In mating A (Fig. 28) there is a daughter who had erythema and intestinal symptoms for three years, yet her sister, who slept in the same bed, has not contracted the disease. On the theory of an intermediary host and a carrier of the disease this is explicable, but the chance of the sister not becoming inoculated is so small that it seems more probable that she resisted infection by virtue of a hereditary capacity.

Moreover, the one thing which seems overwhelmingly to demonstrate an inheritable factor to pellagra is the difference in the course of the disease in different families. In the related matings A and B (Fig. 28), in which none of the parents are affected, we see that the symptoms of the disease are quite mild. The parents in C, B both have had the disease, but in slight form. Of their ten children, only one showed symptoms and these have recurred through three years, but they are not severe. Contrast such families with A (Fig. 15), in which father, mother and three daughters, out of nine children, have died of the disease, and of two affected children of one of them, one died at about the time her mother died with symptoms much like those of pellagra, and the other has the disease in a severe form. It is true that the difference in the course of the disease may be accounted for by a difference in the virulence of the hypothetical specific organism that induces the symptoms, but pathogenic organisms are not the only ones that vary in their qualities, and variations in resistance to disease in the higher animals is as well established a fact as variations of virulence of parasitic microorganisms.

3. BIOTYPES IN REACTION TO PELLAGRA TOXIN

We have seen reason for believing that the inflammations and histolysis of the derma and of the musculovascular coat of the intestine are due to one cause, a toxin that is developed during the attack. Nevertheless, there is in different individuals a striking difference in the reactions of skin, mouth and intestine. Also, the mental symptoms vary greatly in intensity in different persons. It follows from all this that, as we have indeed already seen, the symptom complex shown by different individuals is very varied. We have now to inquire whether this variation occurs at haphazard in the pellagrous population, or whether a particular type of symptom complex tends to run in one family and another type in another family. In biological language, are there strains, or biotypes, that differ in the relative susceptibility, or resistance, of the various organs to the pellagrous toxin?

To get an answer to this inquiry I have gone through the thirty-seven family histories secured by Dr. Muncey in which there is more than one affected person, and looked for families in which there is an exceptionally high or low incidence among pellagrins of a particular symptom. Such families appear at once. Thus, none of the affected individuals of the following families show any of the mental symptoms, such as overactivity, violence, depression, immobility, delirium, which are found in about 10 per cent. of pellagrins generally. From mating C (Fig. 37) there were three affected individuals; in C (Fig. 38) father, two daughters, and their first cousin were affected; in A (Fig. 36), the mother, two children and one grandchild had the disease; in C (Fig. 35), both parents and one child; in B (Fig. 9), both parents and their only child; in B (Fig. 11), father and two children; in C (Fig. 12), both parents and three children; in Fig. 32, two; in B (Fig. 33), mother and all three children; in B (Fig. 29), mother and four children; in D (Fig. 30), mother and daughter; in C (Fig. 31), grandmother, mother and two sons; in B (Fig. 23), mother and two children; in F family, mother and four children; in B (Fig. 8), mother and all four children affected; in family shown in Figure 28, two sisters and their first cousin; in A (Fig. 10), mother and child. It is thus easy to find fairly large sections of affected families in which none of the individuals show mental symptoms. In the following families mental symptoms are more common. In A (Fig. 15) the pellagrous father showed eventual complete mental failure. The mother was feebleminded and mental symptoms were pronounced three months before her death with pellagra. She has a daughter who has no skin trouble, but is feebleminded and suicidal at times, and another daughter is a pellagrin, who, in turn, had a daughter that had severe mental trouble accompanying bowel trouble, and another who died "crazy" at five

years, with erythema and bowel trouble. Thus mental trouble appears in five members of this little group.

Again in A (Fig. 16) the father has recurrent spring attacks of stomatitis, bowel trouble and eruptions on hands and face accompanied by mental symptoms. His son had bowel and stomach trouble with erythema for three years and was insane for a year before he died.

Again, in B (Fig. 25) two sisters had each indigestion followed by bowel trouble, eventually erythema and then marked mental symptoms. In A (Fig. 6) two daughters have dermal and intestinal trouble and also marked mental failure and one grandnephew has nervous symptoms in addition to the erythema. In B (Fig. 7) the mother was already in a hospital for the insane before the physical symptoms appeared. Her father had committed suicide and her mother's brother was a manic-depressive.

More rarely single families will show a marked prevalence of intestinal symptoms with or without eruptions. Thus, in A (Fig. 20) the father died of chronic bowel trouble; his daughter died of "tuberculosis of the bowels, probably pellagrous"; she married a man who had intestinal disorder, probably with skin eruptions, whose father had chronic bowel trouble; two of their three children had "typhoid," so-called, with symptoms like pellagra in one case at least; one died and one recovered. Here are six sufferers from chronic intestinal disorders, only one of whom is typically pellagrous. In a second case the grandfather died of "typhoid fever." Of his four children, one died at 41 of chronic bowel trouble and had (C, Fig. 14) a daughter who had "typhoid" and later eruptions and dysentery; two of her sibs were typical pellagrins. Another one of the grandfather's sons had typhoid in 1869 and in 1913 intestinal and dermal disorders. Here we have four cases of typhoid and bowel trouble without dermal ulcers. In T. F. family the father had typical pellagra and so has one of the children, but one other child died of typhoid and one at 4 years of bowel trouble. The father in mating B (Fig. 19) died of typhoid fever (1895) and so did his brother, who had long been a victim of chronic bowel trouble. The daughter of this mating had pellagra, and of her children, one died in infancy of stomach trouble and "thrush," stomatitis, and another died in infancy of cholera infantum, infantile diarrhea. Thus, in four out of five intestinal trouble only is marked. Of mating B (Fig. 21), the mother of a pellagrin had typhoid and so had her brother, their mother's sister and mother's parents. Other cases might be cited.

Finally, certain strains are characterized by skin troubles chiefly. Thus, in the family represented in Figure 18 the earlier ancestor is characterized by eczema with some indigestion; his two children had eczema, one so severely that her hand had to be wrapped in winter;

a daughter of the latter had eczema all her life. In the family shown in E (Fig. 26) the mother had stomatitis May 1, 1914, loose bowels May 7, with some insomnia, then she developed a typical erythema. Of her five children, three of the boys began at about the same time as their mother to show stomatitis and erythema. But apparently none show marked intestinal derangements. In A (Fig. 17) the mother showed, in March, 1911, typical erythema of hands and forearms followed by stomatitis, diarrhea and general weakness. The same year one of her eldest daughters had erythema of hands and arms lasting for four months. There was no recurrence in 1912, but in 1913 the hands were very red during May and June, but this was attributed to sunburn, despite the fact that she works in the mill all day. Her next younger sister, aged 18 years, had simply erythema of the hands and arms without other symptoms; these symptoms recurred in 1912, but were not present in 1913. The 8-year-old brother had also erythema of the hands and feet and the mouth was sore and there was diarrhea; he had some symptoms in 1912, but none in 1913. In this family the first, and sometimes the only effect, is an inflammation of the skin.

What, now, is the conclusion to be drawn from the facts that in the pellagra families some individuals are characterized only by severe skin symptoms, usually with inflammations of the lining of the mouth, others chiefly by severe intestinal symptoms, especially chronic diarrhea, and others by the predominance of mental symptoms. Why are these symptoms sometimes found associated two at a time or all three together? It seems most probable that we have to do in the different cases with biotypes that differ in the specific resistance or susceptibility of their different organs. That is, we have skin-susceptible biotypes, mouth-susceptible biotypes, intestine-susceptible biotypes, nerve-susceptible biotypes and other biotypes that are resistant in each of these respects or in two or more of them taken together.

An objection may be raised to referring in intestine-susceptible pellagrin families to members who have had "typhoid fever." In justification I may say that many recent cases of pellagra have been diagnosticated as typhoid fever, just as others have been as tuberculosis of the intestine or as eczema. The diagnoses of many physicians and coroners in our southern states have to be interpreted liberally. However, even an indubitable case of typhoid is significant; it implies that the individual tends to react to systemic poisoning by diarrhea, for such is the symptom upon which, combined with rash and high temperature, the diagnosis largely rests. The typhoid is then not significant as an equivalent of pellagra, but as an index of the individual's method of reacting to systemic poisoning, and, as such, it is justifiable to include such individuals in our pedigree of those nonresistant to intestinal symptoms.

IV. Conclusions

. Pellagra is not an inheritable disease in the sense in which brown eye color is inheritable. The course of the disease does depend, however, on certain constitutional, inheritable traits of the affected individual.

Pellagra is probably communicable, but how the communicated "germ of the disease" shall progress in the body depends, in part, upon constitutional factors.

When both parents are susceptible to the disease, at least 40 per cent., probably not far from 50 per cent., of their children are susceptible; an enormous rate of incidence in a disease that affects less than 1 per cent. of the population on the average. While the high incidence is doubtless due to infection, it is also doubtless due to susceptibility, for right among the affected children grow up brothers and sisters who have never shown the symptoms of pellagra. We can understand this on the ground of inheritable differences in constitution of the children, just as brown eyes and blue eyes occur in the same family.

The importance of the constitutional factors is evinced by the difference in the reactions to the toxin of the disease shown by different families. Many families never show mental symptoms, while others usually do. In some families the intestinal symptoms are slight or negligible; in others severe and associated with early death. In some families the skin eruptions amount to little; other families are characterized by severe ulceration and desquamation of the derma. . These family differences have all the characteristics of biotypes or blood lines, and afford the best proof that there is, indeed, a hereditary factor in pellagra.

Carnegie Institute of Washington, Department of Experimental Evolution.

In addition to the references cited in the text, the following may be consulted:

Babcock, J. W.: How Long Has Pellagra Existed in South Carolina, Am. Jour. Insan., 1912, lxix, 185.

KEY TO CHARTS


Square indicates male.


Circle indicates female.


Solid black indicates skin symptoms.

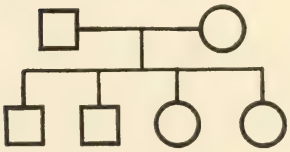

Dots indicate mental symptoms.


Horizontal lines indicate intestinal symptoms


Indicates skin, nervous and intestinal symptoms, usually Pellagra.

d. inf. indicates died in infancy.

Number within square or circle indicates number of children of that sex.


Indicate husband and wife.

Indicate brothers and sisters.

Figure 1

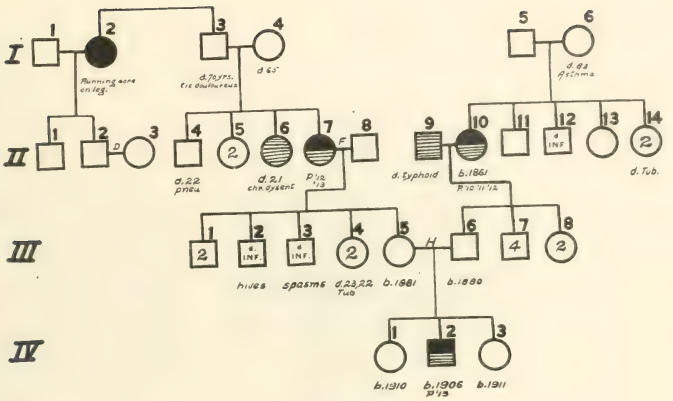


Figure 2

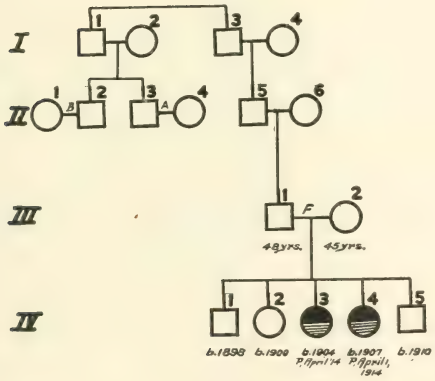


Figure 3

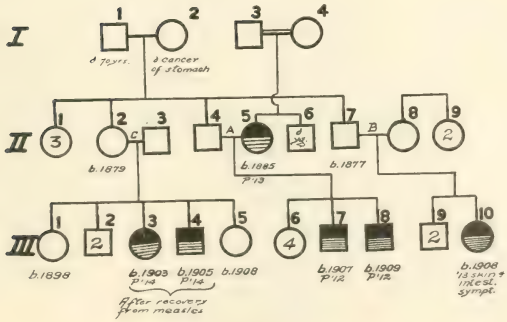


Figure 4

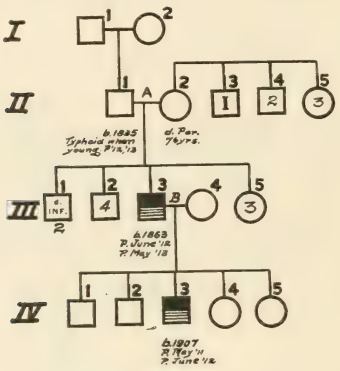
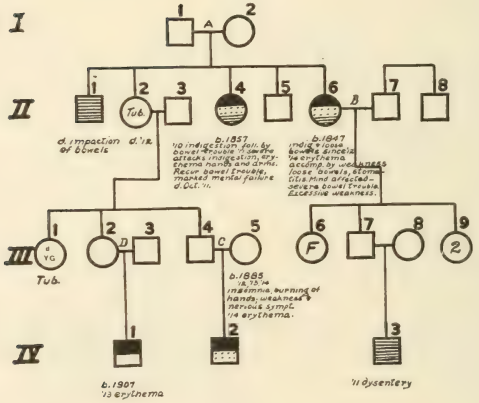


Figure 5



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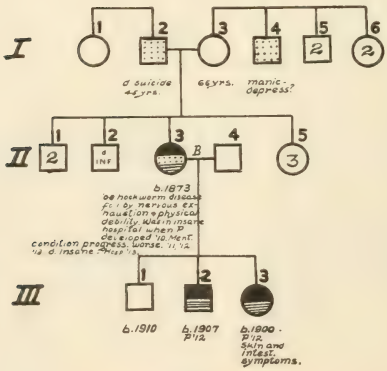

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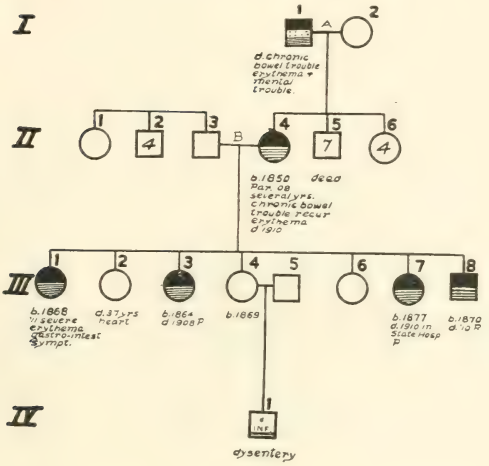
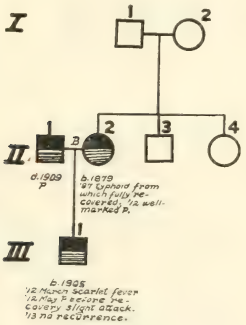


Figure 8



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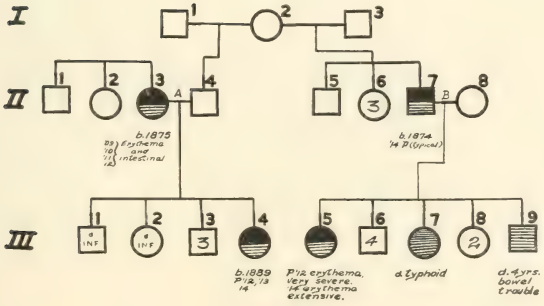

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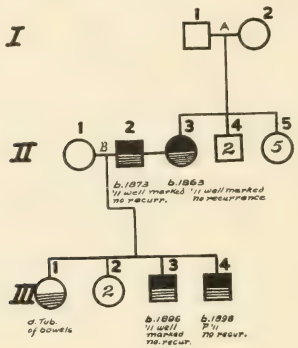

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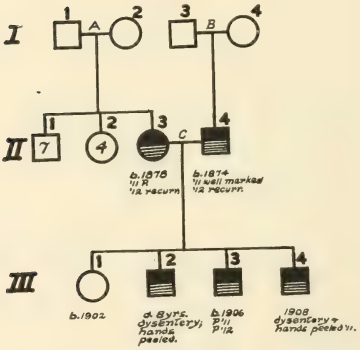

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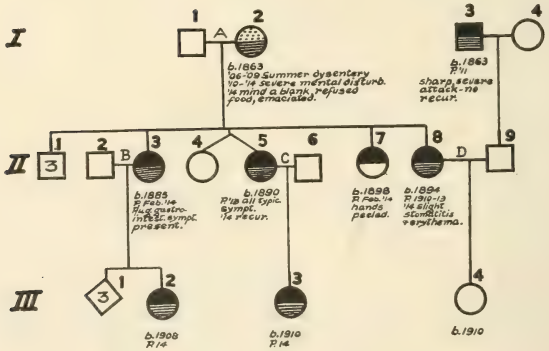
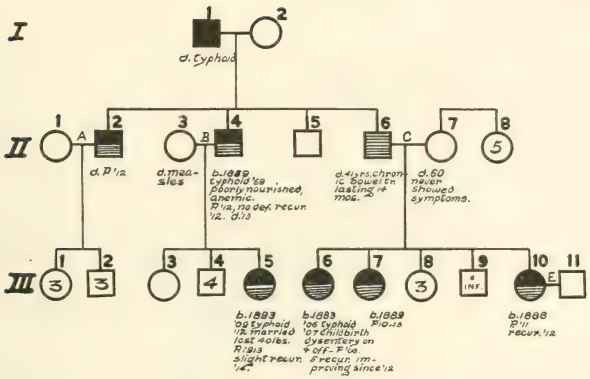


Figure 13



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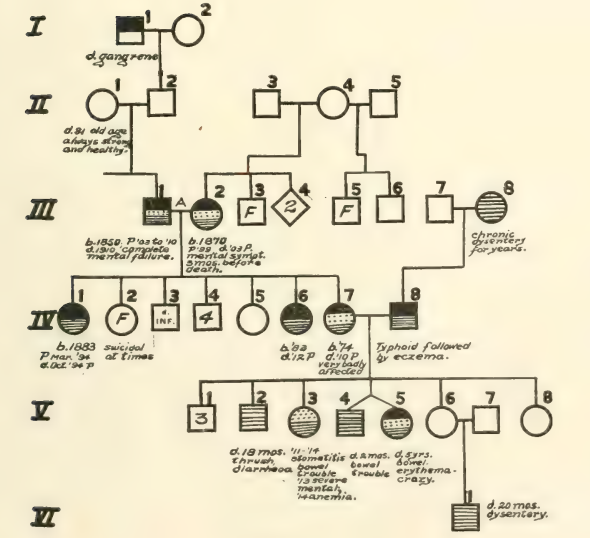

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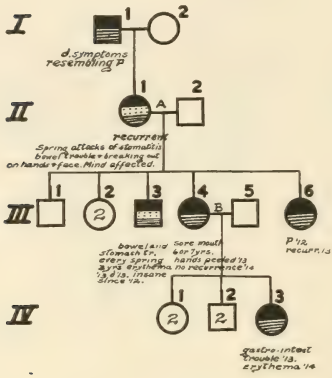

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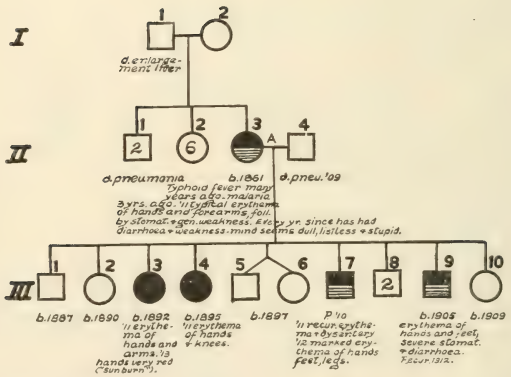
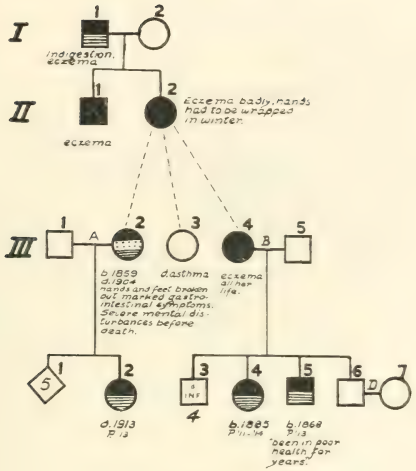


Figure 17.—In this cut III 9 should have been represented as of the female sex and should have been drawn a circle instead of a square.



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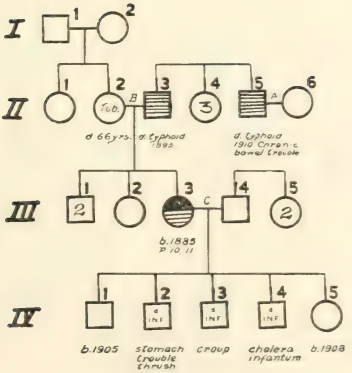

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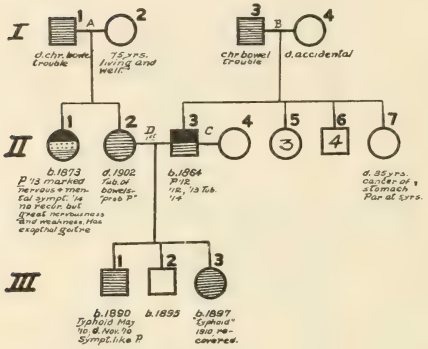

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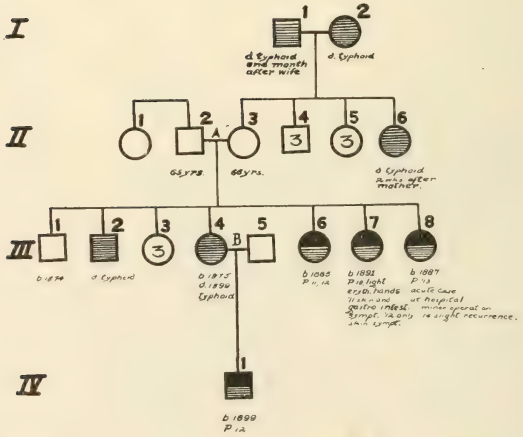

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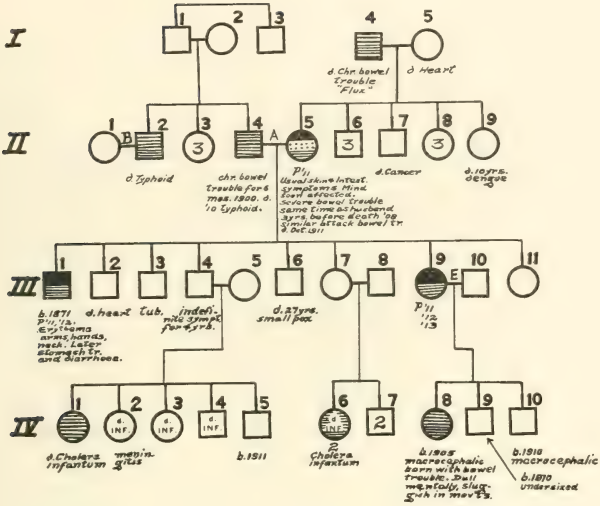

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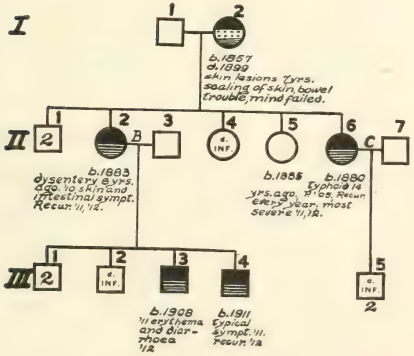

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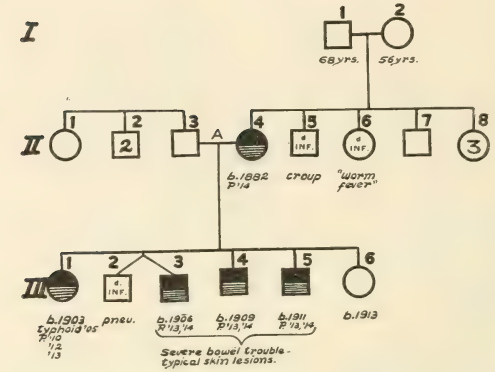

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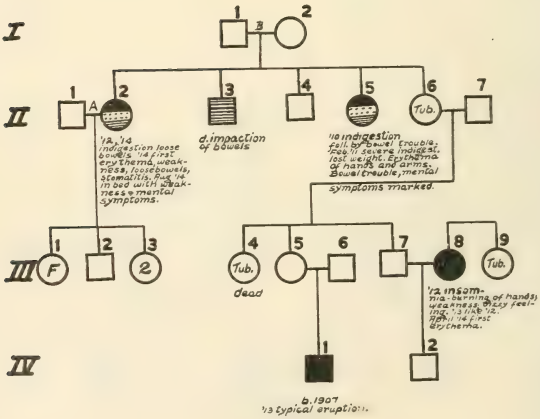

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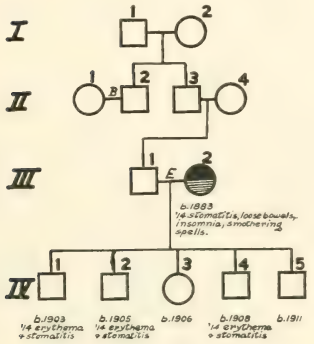

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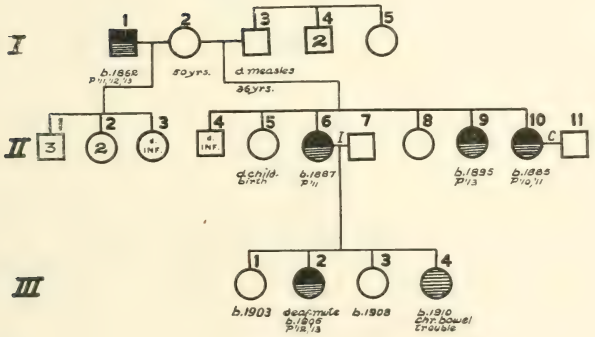

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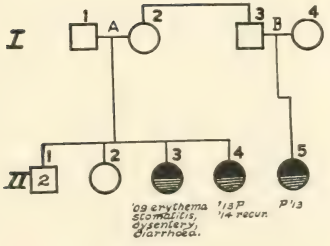

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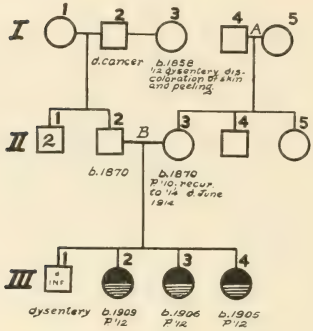
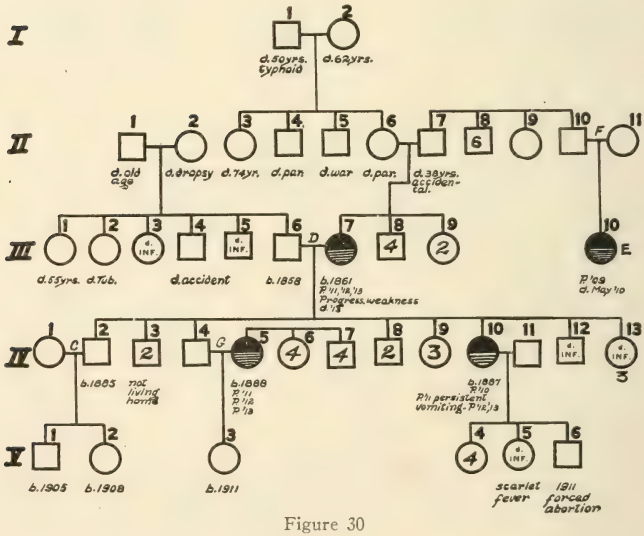


Figure 29.—In this cut the circle II 3 should have been drawn black in upper part and striped below, as in III 2, 3 and 4.



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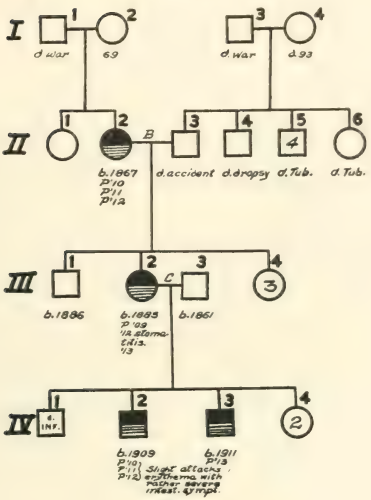

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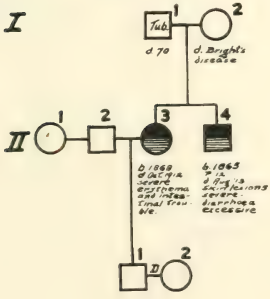

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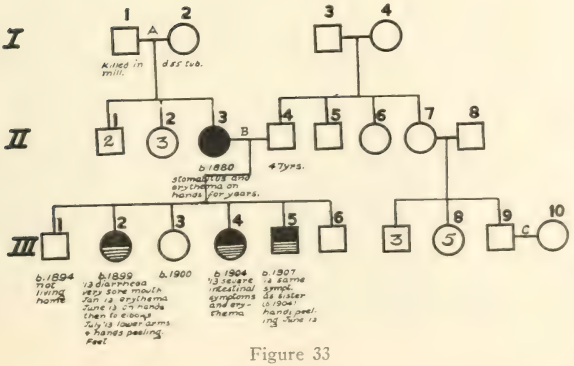

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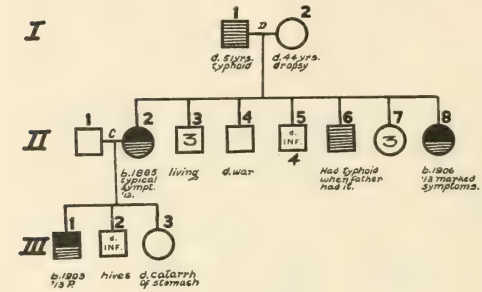
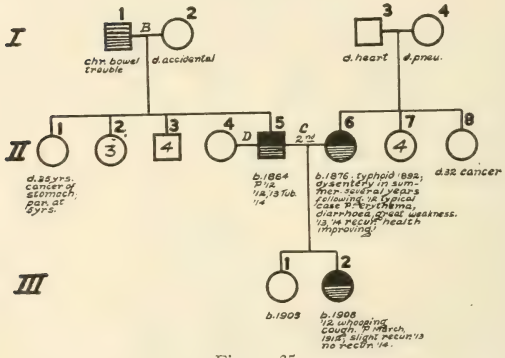


Figure 34



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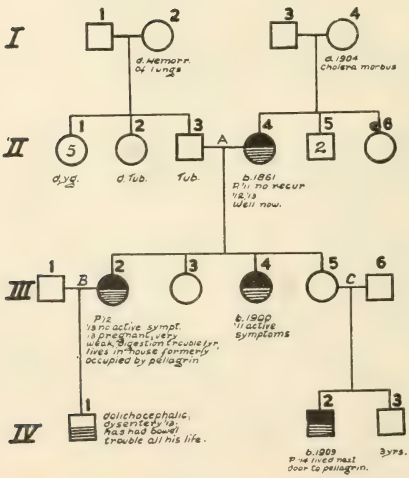

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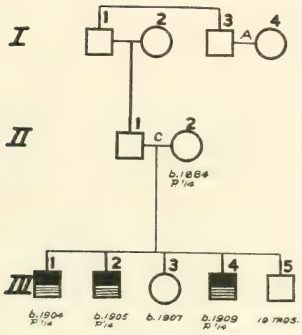

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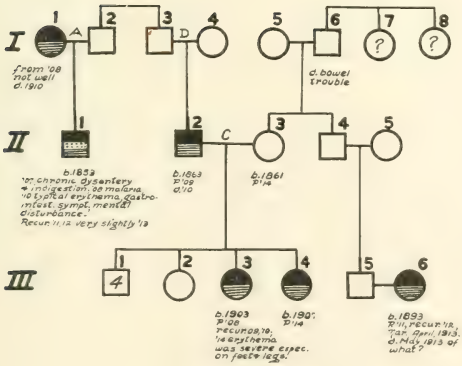

Figure 38

A STUDY OF THE HEREDITY OF PELLAGRA IN SPARTANBURG COUNTY, SOUTH CAROLINA*

ELIZABETH B. MUNCEY, M.D.
COLD SPRING HARBOR, LONG ISLAND, N. Y.

Early in the spring of 1913 the desirability of the study of pellagra from the viewpoint of heredity as a causative factor was brought to the attention of the Thompson-McFadden Pellagra Commission by Dr. Charles B. Davenport, Eugenics Record Office, Cold Spring Harbor, N. Y.

Under the joint patronage of the two offices fieldwork was begun in Spartanburg, June 1, 1913, and continued until Oct. 1, 1913. Through the winter the data collected were carefully reviewed, arranged in family groups and charted. It was found that in many instances more details were necessary, and the Thompson Pellagra Commission in 1914 decided that the results obtained were of sufficient merit to warrant another summer's work. Accordingly, fieldwork was begun May 1, 1914, and continued until Sept. 1, 1914. This year the association of pellagrins with antecedent cases was also carefully noted for comparison.

To study successfully the heredity of any disease it is necessary, first, for the disease to have been known through at least three generations; second, to have access to vital statistics; third, to review family records; and fourth, to interview various members of a family so that statements may be corroborative. The mill villages in South Carolina are not fertile fields for such study, because, first, pellagra has been generally recognized in the South only about twenty-five years, less than one generation; second, in many sections no vital statistics are recorded, or if so, they are so incomplete as to be of little value; third, the majority of families keep no family record; and fourth, while the persons interviewed were in most cases willing to give all the information they could, in many instances they were entirely ignorant of their family histories outside of their own households.

Recognizing the difficulty of presenting a study so imperfect in detail, yet, with a view to establishing a foundation for future study,

* Submitted for publication March 9, 1916.

* From the Eugenics Record Office of the American Genetic Association and the Department of the Laboratories, New York Post-Graduate Medical School and Hospital. This paper forms a part of the Third Report of the Robert M. Thompson Pellagra Commission of the New York Post-Graduate Medical School and Hospital.

we have gathered all possible data, have discarded anything we considered in any way inaccurate, and present herewith the results of the eight months' work.

Every family reported was visited, and as far as possible the members of the households were seen. All possible family history was collected and tabulated. The causes of death, the prevalence of disease, congenital weakness and diseases of the intestinal tract, skin diseases and mental diseases were carefully noted.

Eczema was reported fourteen times, insanity thirteen times, feeble-mindedness twelve times, morphin addiction three times, deaf-mutism ten times, brachydactylism three times, hydrocephalic children twice, dolichocephalic child once, harelip once.

This does not show a larger proportion of any disease than one might expect from the study of an equal number of individuals taken from any nonpellagrous community of similar status.

The history of forty-five colored pellagrins in thirty-five households was taken. Of these, there were twenty-eight female and seventeen male. They knew so little of their family history—many not even knowing their fathers' names—that the study of inheritance was not undertaken.

The family histories of 555 white pellagrins were studied, which involved a partial history of 1,872 households, 786 of which were visited.

The families were grouped according to the number of pellagrins into six groups (see Table 1) as follows:

Group I, one pellagrin in family.
Group II, two pellagrins in family.
Group III, three pellagrins in family.
Group IV, four pellagrins in family.
Group V, five pellagrins in family.
Group VI, more than five pellagrins in family.

In Group I, one pellagrin in a family, there were seventy-three parents with 248 children—201 living and forty-seven dead, 172 living at home with the parents. None of these had recognized pellagra, although fourteen children died with intestinal trouble after the mother developed pellagra. One died with measles and dysentery, aged 11 months; seven with bowel trouble, ages ranging from 3 to 21 months; one with thrush and pneumonia, aged 1½ years; one with hives, aged 3 months; one with hives and stomach trouble; one with dysentery and rash, aged 2 years; one with rash, sore mouth and diarrhea, aged 14 months.

Dr. Simonini recognizes two kinds of pellagra in childhood: (1) pellagra with cutaneous symptoms; (2) pellagra without cutaneous

symptoms. In all probability the fourteen cases cited above would have been classed by him as pellagra without cutaneous symptoms.

In one of these families, the grandfather, 75 years of age, has had indigestion for years. The great-grandfather died of tuberculosis of the bowels. Several members of the grandmother's family died of

TABLE 1.—Distribution of Pellagrins and the Number of Families, Households and Individuals in Each Group

Group	Pellagrins			Families	Households	Individuals
	Female	Male	Total			
I.....	83	22	105	105	626	2,259
II.....	72	30	102	51	306	1,056
III.....	71	31	102	34	380	1,027
IV.....	51	29	80	20	80	637
V.....	78	32	110	22	309	1,073
VI.....	39	17	56	7	171	644
Total.....	394	161	555	239	1,872	6,696

TABLE 2.—The Relative Proportion in Which the Different Members of a Family Were Affected With Pellagra

Group	Mothers	Fathers	Wives*	Daughters	Sons	Total
I	63	10	7	12	13	105
II.....	45	14	..	27	16	102
III.....	40	17	10	21	14	102
IV.....	27	11	4	20	18	80
V.....	49	12	9	20	20	110
VI.....	21	10	2	18	5	56
Total.....	245	74	32	118	86	555
Rate per cent.	44	13.4	5.8	21.3	15.5	100

* Married women who have not borne children.

typhoid. The mother, Case 18, had typhoid in 1907 and developed pellagra in 1910. One child, born in 1911, died at the age of 3 months of bowel trouble; four other children are living and well.

In one family the grandmother died with chronic bowel trouble. Maternal uncles died with dysentery. Mother, Case 612, developed

pellagra in 1910. One daughter died in infancy with hives. One son died in infancy with bowel trouble. Seven other children are living and well.

In one family the grandmother died insane. In the mother's fraternity there were four infant deaths, and three births before term. The mother, Case 37, developed pellagra in 1908 and has had yearly recurrences ever since, always accompanied with severe mental symptoms. One son died at 2 years of age with dysentery and rash, one daughter died at 1½ years of age, with thrush and pneumonia. Two girls, aged 12 and 8, are living and unaffected.

In Group I, it is possible to trace an inherited weakness from the grandparents in twelve cases:

Case 18, one great grandfather died with tuberculosis of bowels.
Case 606, one grandfather died of typhoid.
Case 687, one grandfather died insane.
Case 612, one grandmother died with chronic bowel trouble.
Case 54, one grandmother died with dysentery.
Case 541, one grandmother died with dysentery.
Cases 693, 521 and 281, three grandmothers died of typhoid.
Case 37, one grandmother died insane.
Case 611, one grandmother died with indigestion.

In Group II, two pellagrins to a family, the fifty-nine parents had thirty pellagrous children and 153 nonpellagrous. There were thirteen pellagrous children with nonpellagrous parents, and forty-three brothers and sisters not pellagrous. Four children died after their mother developed pellagra. One died with hives at 4 months; one with dysentery at 5 months; and twins miscarried.

Inherited weakness was traced from the grandparents in eight cases:

Case 713, one great grandmother died with colic and the grandfather had pellagra in 1911, 1912 and 1913.
Case 81, one great-grandmother died with stomach trouble, and the grandmother developed pellagra in 1911.
Cases 107, 130 and 703, three grandmothers were pellagrins.
Case 160, one grandmother died insane.
Case 944, one grandfather died of pellagra in 1912.
Case 601, one grandfather died with typhoid.

In Group III, three pellagrins to a family, the fifty-seven parents had twenty-four* pellagrous children and 119 nonpellagrous. Twenty-one children were pellagrous in the same household with unaffected parents and sixty unaffected brothers and sisters. Four children died after their mother developed pellagra, one dying with marasmus, one with bowel trouble, one with hives, one with dysentery and hands peeling.

*Those pellagrins designated as wives in Table 2 are included here in the group of children.

In one family the grandfather committed suicide. Insanity ran in the grandmother's family. The mother, Case 25, developed pellagra in 1910 with marked mental symptoms. She died in 1913 in an asylum. Two children, one boy and one girl, developed pellagra in 1912. The youngest child, 4 years of age, is unaffected.

Inherited weakness is traced to grandparents in five cases:

Case 25, one grandfather committed suicide, and several members of the grandmother's family were insane.

Case 162, one grandfather died with typhoid; the father and son were both pellagrins.

Case 366, one grandfather died with bowel trouble; the mother and daughter were both pellagrins.

Case 526, one paternal grandfather died of bowel trouble; the father, daughter and mother were pellagrins.

Case 432, one grandfather died in 1901 of pellagra and insanity; mother and daughter are both pellagrins.

In Group IV, four pellagrins to a family, thirty-eight pellagrous parents had twenty-five pellagrous children and eighty-one nonpellagrous, while seventeen children were pellagrous in the same household with unaffected parents and thirty-eight unaffected brothers and sisters.

Inherited weakness was traced to grandparents four times:

Case 55, one great-grandmother died in 1904 with bowel trouble; the grandmother developed pellagra in 1911, the mother in 1912, and the son, aged 2 years, was dolichocephalic. His bowels were bad from birth. One great-grandson from another line of descent developed pellagra in 1913.

Case 83, one grandmother developed pellagra in 1910; the mother developed pellagra in 1909 and two sons developed the disease in 1913. One son died in infancy, cause unknown.

Case 132, one grandfather died in 1909 with pellagra and insanity. The grandmother developed pellagra in 1910. They had fifteen children, six of whom died in infancy. None of the children developed pellagra, but two grandchildren developed it in 1913.

Case 565, one maternal grandfather died of pellagra in 1909. The mother and son developed it in 1911 and the father, whose family history is negative, developed it in 1912.

In Group V, five pellagrins to a family, the sixty-one pellagrous parents had thirty-eight pellagrous children and 140 nonpellagrous. Eleven children were pellagrous in the same household with unaffected parents, and thirty-four unaffected brothers and sisters. Inherited weakness was traced to grandparents in three cases.

Case 308, one grandmother died of pellagra in 1900. The mother developed pellagra in 1910, her two sons in 1911, and the mother's sister in 1905. This sister had twins, who died three weeks after birth, and no other children.

Case 392, one grandfather died of chronic bowel trouble. The mother died of pellagra in 1910. Two daughters died of pellagra in 1908 and 1910. One son died of pellagra in 1910. One daughter, living, developed pellagra in 1911 and has recurrence yearly. She had eight children, two of whom died in infancy. (Fig. 19, R Family for other case.)

In Group VI, more than five pellagrins to a family, the thirty-one parents had twenty pellagrous children, and sixty-five nonpellagrous. Five children were pellagrous in the same household with unaffected parents and twenty-one unaffected brothers and sisters.

TABLE 3.—Comparative Incidence of Pellagra Among Children With Nonpellagrous Parents, With One Pellagrous Parent and With Two Pellagrous Parents

Group	Parents		Children	
	Pellagrous	Nonpellagrous	Pellagrous	Nonpellagrous
With nonpellagrous parents:				
I	0	58	32	84
II	0	41	23	43
III	0	81	45	60
IV	0	30	17	38
V	0	19	11	34
VI	0	10	5	21
Total	0	239	133	280
With one pellagrous parent:				
I	73	...	0	172
II	55	...	30	134
III	47	...	20	106
IV	26	...	17	54
V	55	...	38	124
VI	21	...	15	42
Total	277	...	120	632
With both parents pellagrous:				
I	4	...	0	19
II	10	...	4	13
III	12	...	8	27
IV	6	...	0	16
V	10	...	10	23
VI	0	...	0	0
Total	42	...	22	98
Grand total	319	...	275	1,010

In Table 3 there are twenty-one matings of forty-two parents with both parents pellagrous. They have 120 children, twenty-two pellagrous and ninety-eight nonpellagrous. There are 277 matings of 554 parents with only one parent showing pellagra. They have 752 children, 120 pellagrous and 632 nonpellagrous. If pellagra were an heredi-

TABLE 4.—Relationship Existing When There Were Two or More Pellagrins in a Family

Relationship*	Groups						
	I	II	III	IV	V	VI	All Groups
M and D only	..	12	7	3	6	5	34
M and S only	..	4	3	1	1	1	10
M, D, and S	..	..	4	4	4	1	13
M and any child	..	17	14	8	11	7	57
F and D only	..	6	2	1	3	1	13
F and S only	..	2	..	1	..	..	3
F, D, and S	..	..	1	..	..	..	1
F and any child	..	8	3	2	3	1	17
M, F and D	..	..	..	..	..	2	2
M, F and S	..	..	3	2	..	..	5
M, F, D and S	..	..	..	..	..	1	1
M, F and children	..	..	3	2	..	3	8
Total number of individuals of each class:							
Mother	63	45	40	27	49	21	245
Father	10	14	17	11	12	10	74
Daughter	12	27	21	20	20	18	118
Son	13	16	14	18	20	5	86
Total	98	102	92	76	101	54	523

* In this table M signifies mother; F, father; D, daughter, and S, son.

tary trait we might expect in the first instance ninety pellagrous children instead of twenty-two, and in the second instance at least 158 instead of 120. The 133 pellagrous children from unaffected parents would also demand explanation. Where did their susceptibility to the

disease originate? Again, the fact that in almost every instance the second or the third member of a family developed pellagra within a few weeks or months of the time of the incident case strengthens the indication that the disease is not transmitted by heredity.

In Table 4 there are 245 mothers in all groups, sixty-five, or 26.3 per cent., with pellagrous children, and 180, or 73.5 per cent., without pellagrous children, nearly three times as many without as with pellagrous children.

TABLE 5.—Relationship of Pellagrins in Families With Pellagra in the Third Generation

1 grandmother (1911-1913)	.....	1 granddaughter (1914)	Direct
2 grandmothers (1893-1911) (1910-1913)	.....	1 grandson (1913)	Direct
1 grandfather (1912)	Mother (1913-1914)	2 granddaughters (1913-1914)	Direct
1 grandfather (1909)	[Grandmother] (1911)	2 granddaughters (1913)	Direct
1 grandfather (1912-1913)	Father (1912-1913)	1 grandson (1911-1912)	Direct
1 grandfather (1901)	Mother (1907-1913)	1 granddaughter (1911-1913)	Direct
1 grandmother (1910-1912)	Mother (1909-1913)	2 grandsons (1910-1913)	Direct
1 grandfather (1908)	Mother (1904-1913)	2 grandsons (1912)	Direct
1 grandmother (1910-1912)	Mother (1909-1913)	2 grandsons (1910-1912) (1913)	Direct
1 grandmother (1900)	2 mothers (1905) (1910-1911)	2 grandsons (1911-1912)	Direct
1 grandmother (1910-1914)	4 daughters (1910) (1913) (1914)	2 granddaughters (1914)	Direct
1 grandfather (1913)	Son-in-law (1912-1913)	1 granddaughter (1914)	Direct and indirect
1 grandfather (1910-1912)	Daughter-in-law (1912-1913)	2 grandsons (1913) (1914)	Direct and indirect
1 grandfather (1909)	Daughter and son-in-law (1911-1913) (1912)	1 grandson (1911)	Direct and indirect
1 grandmother (1910)	Son and daughter-in-law (1910-1912) (1910)	3 grandchildren (1912)	Direct and indirect
There are also 1 step-grandfather (1911-1914)	3 stepchildren (1910) (1910) (1913)	2 step-grandchildren (1910) (1913)	
1 step-grandmother (1912)	1 stepdaughter (1910-1914)	3 step-grandchildren (1912)	

There are seventy-four fathers in all groups, twenty-five, or 33.8 per cent., with pellagrous children, and forty-nine, or 66.2 per cent., without pellagrous children, nearly twice as many without as with pellagrous children. The frequency with which mother and daughter only are affected is nearly three and one-half times the frequency with

which the mother and son only are affected. The frequency with which father and daughter only are affected is four times that when father and son only are affected. There is no definite explanation of this excessive number of daughters affected, it may be partially explained by the greater prevalence of pellagra in girls between the ages of 15 and 20. This is not borne out, however, by the number of pellagrins of the two sexes in our study where we have 118 daughters and eighty-six sons. The question arises whether the closer contact of the daughter with parents in the mill villages studied may not be a large factor in this excess. The boys from the time they can walk until the time when they go to work in the mill spend most of the time, except when sleeping, on the streets.

TABLE 6.—Causes of Death in Adults

Groups	I	II	III	IV	V	VI	Total
Typhoid	..	32	17	9	8	26	92
Chronic bowel trouble or dysentery	3	10	9	7	5	14	48
Indigestion	..	5	6	3	5	19	38
Tuberculosis	..	12	2	10	12	17	53
Heart	..	8	1	4	2	10	25
Paralysis, without specified cause	..	15	2	6	3	5	31
Kidney trouble	..	8	4	3	2	3	20
Pneumonia	..	4	4	3	3	3	17
Dropsy, without specified cause	..	6	2	1	1	6	16
Cancer	..	4	1	2	2	3	12
Suicide	1	..	..	1	..	5	7
Asthma	..	4	..	2	..	1	7
Rheumatism	..	4	2	..	..	1	7
Epilepsy	..	1	4	7	..	..	12

There are fifteen families in which grandparents are affected. These have been counted as members of one family, although the descent is not always in a direct line. The relationships are shown in Table 5.

If there were a sufficient number of cases, this table would appear to indicate heredity, but when we consider the 596 parents in our study and find that they should have had over 2,000 grandfathers, the number of affected grandparents, namely, fifteen, is an insignificant quantity.

In every instance except the last two cases, the disease has occurred coincidentally or within a year or two in the grandparents and the other members of the family. In every instance except the two last men-

tioned, there has been direct family contact. Lombroso says: "Often the influence of heredity is not demonstrable because the grandparental influence escapes the slight interest of the poor country people, although atavistic heredity is more common than from father and mother." Strambio wrote that the greater part of pellagrins are born of pellagrous parents, and that the offspring of these has a decided disposition for taking the disease. A study of these same families during twenty or thirty years would be necessary to confirm this statement.

Accurate death reports were impossible to obtain, but wherever the causes of death were actually known they were recorded.

TABLE 7.—Causes of Infant Death

Diseases	Groups						
	I	II	III	IV	V	VI	Total
Bowel trouble or dysentery	8	2	4	4	15	5	38
Whooping-cough	3	2	..	..	6	1	12
Hives	3	1	3	..	2	2	11
Pneumonia	2	2	1	..	4	2	11
Catarrh of stomach	3	2	1	..	2	..	8
Cholera infantum	1	1	2	1	..	2	7
Thrush	3	..	..	..	2	1	6
Marasmus	1	2	1	..	..	1	5
Meningitis	2	..	..	1	..	1	4
Measles	..	1	1	..	..	1	3
Peritonitis	1	..	..	..	..	1	2
Born dead	..	..	..	..	10	3	13
Unknown	62	35	26	12	23	24	182
Total known	27	13	13	6	41	20	120

No record was made of deaths from diphtheria, scarlet fever, malaria, measles, erysipelas or smallpox.

Table 6 is of value only in showing the relatively high proportion of typhoid fever and stomach and bowel trouble in the families in which there were more than one pellagrin.

Under the date of Oct. 23, 1909, Acting-Assistant Surgeon Sams[1] of the U. S. P. H. S. reported from Charleston as follows: "Pellagra, as such, has but recently been recognized in this city, the first case

1. Sams: Pub. Health Rep., 1909, xxiv, 1657.

having come under treatment in March, 1908. There is a very general impression among the local physicians that pellagra has existed in the city for probably twenty years or more, and been incorrectly diagnosed as eczema, dysentery, intestinal tuberculosis, etc., with dementia as a complication, or the reverse."

J. W. Babcock,[2] M.D., superintendent of State Hospital for Insane, Columbia, S. C., adds several others: "syphilis, malaria, acute delirium, hookworm, dermatitis exfoliativa, tuberculosis of the skin, liver spots, scurvy, neurasthenia, meningitis, nurse's sore mouth, sprue, meningo-encephalitis, neuritis, etc."

This table simply shows a record of the infant deaths in the households visited. It was impossible to get any account of the number or causes of infant death outside of the households of those visited. It is worthy of note that of the 120 deaths for which causes were assigned, there were seventy-two suggestive of stomach or intestinal disease.

C. Lombroso[3] in 1898 wrote:

> There are pellagrous and pseudopellagrous conditions which are even harder to diagnosticate than complicated pellagra, because the pellagra, while it is present, has not been able fully to develop. Here belongs a type which I designate hereditary pellagra. It occurs in a very severe and a very mild type. It is noticeable at the end of the second year of life, rarely with desquamation, more frequently with pains in the epigastrium, pyrosis, "Heisshunger," uncertain gait, timidity, diarrhea, a yellowing of the skin as in malaria-cachexia, retardation and cessation of development; but later all symptoms of pellagra appear and resist strongly any treatment. . . . In many cases I found a bad formation of the skull, exceptional brachycephaly or dolichocephaly, fleihende (retreating?) forehead, badly set ears, asymmetry of face, anomalies of genitalia.

A complete census was taken in two mill villages. The children in every family, whenever possible, were inspected, and no difference such as Lombroso mentions could be seen between those in pellagrous homes and those in nonpellagrous homes.

In every group except Group I the ratio of adult women with children to adult women without children is about three to one. There are four sets of pellagrins, namely, adult females without children, adult males with children, girls and boys under 20, of whom the number in each group is almost the same. We have not been able to attach any significance to this equality in number. In all groups the average age of incidence in boys is 11 years, in girls 14 years, in adult females 35 years, and in adult males 52 years. The earliest age at which the disease developed was in a boy of 15 months, and the oldest was in a man of 82 years, while in women and girls the youngest was 18 months and the oldest 78 years.

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2. Babcock, J. W.: A Study of Local Medical History, Am. Jour. Insan., 1912, lxix, 1.

3. Lombroso, C.: Die Lehre von der Pellagra, p. 116.

TABLE 8.—Pellagrins Under Twenty Years of Age, and the Relative Proportion of Adults Who Have Borne Children

	Groups						
	I	II	III	IV	V	VI	Total
Adult females with children	63	45	40	27	49	21	245
Adult females without children	10	13	15	10	16	6	70
Girls under 20 years	10	14	16	14	13	12	79
Total female	83	72	71	51	78	39	394
Adult males with children	10	14	17	11	12	10	74
Adult males without children	2	1	2	1	5	1	12
Boys under 20 years	10	15	12	17	15	6	75
Total male	22	30	31	29	32	17	161

TABLE 9.—Association of Pellagrins With Antecedent Cases

	Groups						
	I	II	III	IV	V	VI	Total
Association outside family	37	19	12	7	14	8	97
Association within family	0	36	46	51	55	33	221
Endemic neighborhood	46	20	8	3	19	3	99
Negative history	22	27	36	19	22	12	138
Total number pellagrins	105	102	102	80	110	56	555

ASSOCIATION STUDY

An effort was made to find to what extent pellagrins had associated with the antecedent cases. The pellagrins studied have been grouped as follows:

1. Those who associated with pellagrins outside of the family.
2. Those who associated with pellagrins in the family.
3. Those who could give no history of association, but lived in endemic neighborhood.
4. Those who could give no history of contact.

A negative history does not mean that there had been no contact, but only that the pellagrin does not know of contact.

Table No. 9 shows positive association in 318 cases, with a possible association in the ninety-nine cases more living in endemic neighborhoods, against 138 with negative history.

CONCLUSION

An analysis of the data collected shows no evidence of direct heredity. There may, however, be an hereditary predisposition to the disease in those families in which chronic gastro-intestinal symptoms have existed for several generations. The relatively high proportion of gastric and intestinal diseases among pellagrous families would seem to substantiate this hypothesis. Of the 105 families in which there is only one case of pellagra, only three give history of intestinal or skin diseases in the ancestors, and only 1 gives history of antecedent insanity. With this predisposition to the disease, direct contact or life in endemic sections might be the exciting factor necessary for its development.

The abstracts of family histories and charts which follow will serve to show the manner of studying family groups.

The symbols used in the charts are the following:


Square indicates male.

Square with PI inside indicates male pellagrin.

Square with question mark inside indicates pellagra questionable.


Circle indicates female

Circle with PI inside indicates female pellagrin.


Diamond indicates sex unknown.

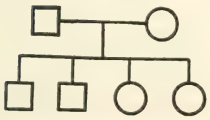
d. inf. indicates died in infancy.

Number within square or circle indicates number of children of that sex.

Year number under symbol indicates incidence and recurrence of pellagra.

A indicates alcoholic; B indicates blind; D indicates deaf; D M indicates deaf mute; E indicates epileptic; F indicates feebleminded; I indicates insane; T indicates tubercular; d indicates died; P indicates paralysis.

Each horizontal line represents a generation, the symbols for the individuals of a fraternity (full brothers and sisters) being on the same horizontal line. This line is connected by a vertical line to a line joining the symbols of father and mother.


Indicate husband and wife.

Indicate brothers and sisters.

Broken lines indicate illegitimacy.

Hand indicates earliest recognized case in family.

Fig. 1.—This chart gives an explanation of the symbols that are used in the succeeding illustrations of this article.

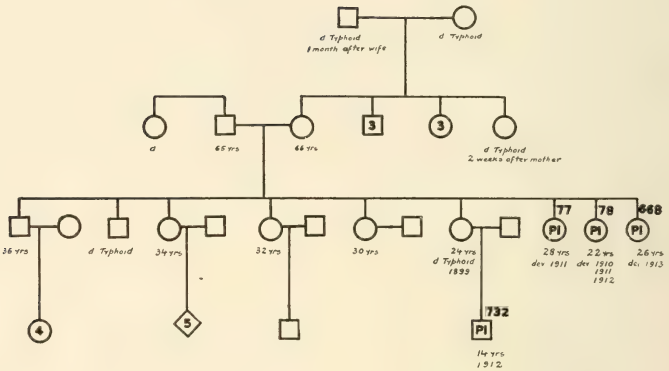


Fig. 2 (N Family).—The N family is in comfortable circumstances, two of the daughters being teachers. The first to develop pellagra was Pellagrin 78, B. N., aged 22, who clerked in a store from 1906 to 1909 and attended a "female college" from 1909 to 1911. She is now teaching. In June, 1910, pellagra developed with light erythema on hands, and in 1911 she had skin and gastro-intestinal symptoms; in 1912 only skin symptoms. Pellagrin 77, G. N., aged 28, did the housework at home and slept in the same room with her sister. In the spring of 1911 she developed pellagra, which recurred in 1912, but was not present June 30, 1913, when visited.

Pellagrin 668, T. N., aged 26, a teacher, developed an acute attack of pellagra in 1913 at Good Samaritan Hospital, while there for a minor surgical operation. She had a very slight recurrence in 1914. The parents of these young women are living and well.

Pellagrin 732, E. S., aged 14, a nephew, lived with his aunts for six months in the winter of 1911 and developed pellagra the next year, 1912. He was not seen in 1913 or 1914 and it is not known whether he had a recurrence. His mother died in 1899 with typhoid fever. There were five deaths in this family from typhoid (see chart).

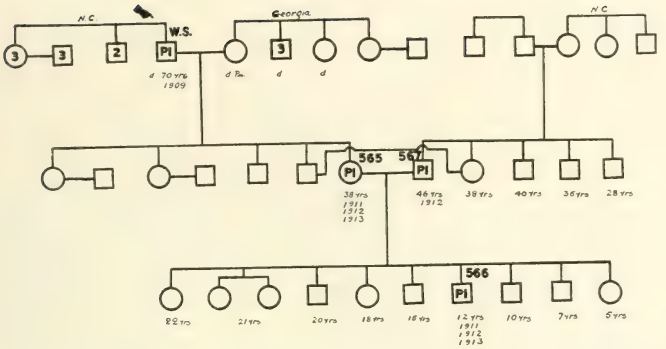


Fig. 3 (B. S. Family).—The father of Pellagrin 565, W. S., and his family lived in North Carolina. Mortality statistics were not available. W. S. died, aged 70 years, of pellagra, in North Carolina in 1909. He was nursed by his daughter, Pellagrin 565. His wife had died previously from pneumonia. Her family is in Georgia. Nothing definite could be learned concerning his illness. His daughter said that the gastro-intestinal symptoms were most pronounced, but he had also marked discoloration over hands, feet and shoulders. Three months previous to death there were marked mental symptoms.

Pellagrin 565, I. B., came with her husband to S, mill village, in 1910. She had good health until 1911. Then erythema, stomatitis and diarrhea developed. She had a typical recurrence in 1912 and very slight recurrence in 1913. Her husband, Pellagrin 567, W. F. B., aged 46 years, a mill worker, developed the disease in 1912. He did not show any recurrence of the erythema, but for four months in 1912 his other symptoms were quite severe. He had always lived in North Carolina, and his family is still there and are not known to have any disease. His father and mother and his aunts and uncles are all living and well.

They have ten children, ranging in ages from 22 years to 5 years. Only one showed pellagra, Pellagrin 566, H. B., who developed it the same time his mother did, and had recurrences in 1912 and 1913. He seemed to be as well as the other children previous to the attack.

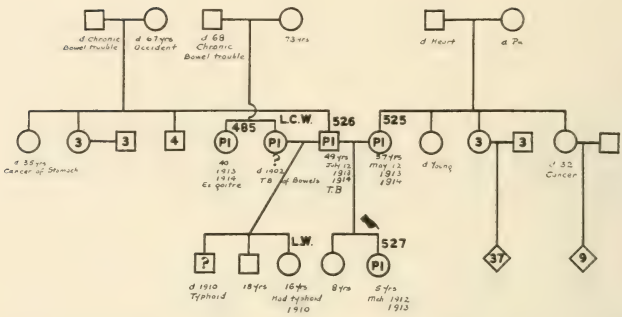


Fig. 4 (W1. Family).—L. C. W., the first wife of Pellagrin 526, died in 1902 of tuberculosis of the bowels. Since pellagra has been recognized, the family thinks the cause of death was pellagra instead of tuberculosis. She left three children, one of whom, L. W., had typhoid fever May 28, and died in November, 1910. His symptoms were very similar to those of pellagra. One daughter, L. W., had typhoid (?) at the same time, but recovered in two months. One son, aged 18 years, is living and well.

Pellagrin 485, S. C., aged 40 years, sister of L. C. W., developed a well-marked case of pellagra in 1913. She had marked nervous and mental symptoms. There was no recurrence of erythema in 1914, but there was great nervousness and weakness. As she has exopthalmic goiter in a pronounced form, these symptoms may be due to that condition. Her mother is living and well, but her father died several years ago with chronic bowel trouble. There has been and is close association between this family and the family of Pellagrin 526.

Pellagrin 527, E. W., aged 5 years, daughter of second wife of Pellagrin 526, had whooping-cough in January and February, 1912, and in March, before she recovered, had a well-developed attack of pellagra. There was a slight recurrence of symptoms in 1913; no recurrence in 1914. Her sister, 8 years of age, shows no symptoms.

Pellagrin 525, B. W., second wife of Pellagrin 526, aged 37 years, had typhoid in 1892 and dysentery for several years following, in the summer. In May, 1912, she developed a typical case of pellagra with erythema, diarrhea and great weakness. The diarrhea continued through the winter. There were recurrences in 1913 and 1914. Her general health is improving, however. There is no history of any bowel trouble in her family. Her father died with heart trouble and her mother with pneumonia. One sister died young, cause unknown, and one married sister died, aged 32 years, with cancer of stomach. She fell and injured herself and the cancer is supposed to have resulted from the injury.

Pellagrin 526, C. J. W., aged 49 years, developed pellagra in July, 1912, and had recurrences in 1913 and 1914. He was also tubercular and became very much emaciated and excessively weak. He was in hospital for treatment in 1913; much improved in 1914. One of his sisters died, aged 35 years, of cancer. She was paralyzed at 5 years and used a wheeled chair for 30 years. The father of Pellagrin 526 died with chronic bowel trouble and his mother was thrown from a carriage when 67 years old and died from result of injury.

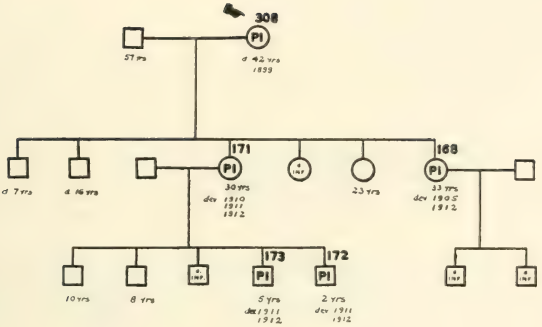


Fig. 5 (J. Family).—Pellagrin 308, E. D., mother of Pellagrin 168, died, aged 42, in 1899, on a farm in Spartanburg County. She had been in bad health for twenty years, and had skin lesions for seven years before death. She had scaling of skin of hands and severe bowel trouble. Her mind failed two years before death. The doctor who attended her thinks she undoubtedly had pellagra. The father of Pellagrin 168 is still living, aged 57 years. No one in his family is known to have pellagra. There were six children. Two boys died young—causes unknown. One daughter died in infancy; one unmarried daughter is living, apparently normal. The two remaining daughters are pellagrins.

Pellagrin 168, C. J., aged 33, worked in the mill, but for the last eight years has done housework. She cared for her mother in her last illness. All three sisters were at home during this time. Pellagrin 168 had typhoid fourteen years ago, the year following her mother's death. In June, 1905, the first typical pellagra symptoms were noticed. There has been a recurrence every year, but symptoms were most severe in 1911 and 1912. She had two sons, who died when a few weeks old; no other children. Her sister, Pellagrin 171, B. J., aged 30 years, had a bad attack of dysentery eight years ago, after the second child was born. She has not been strong since. In March, 1910, she lost her baby; did not gain health afterward; in October of the same year showed typical skin and intestinal symptoms; had recurrence in 1911 and 1912. Her husband's family is said to be free from pellagra. They had five children: two sons, aged 10 and 8 years, living and well; one son died in infancy. Pellagrin 173, W. J., had severe illness when 21 months old. He had spasms and does not talk well. His first pellagra symptoms, erythema and diarrhea, appeared in July, 1911, with recurrence in June, 1912. Pellagrin 172, A. J., was 15 months old when he showed typical symptoms in June, 1911; had a very light attack with recurrence in 1912.

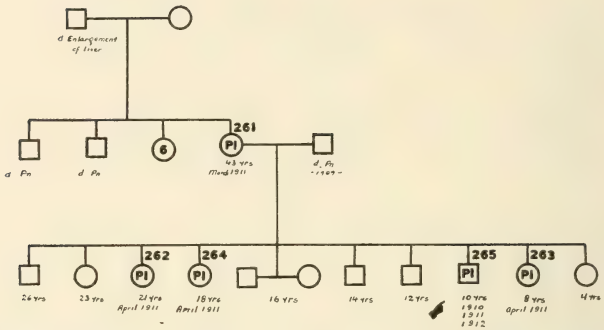


Fig. 6 (Sc. Family).—Pellagrin 261, Mrs. J. S., came originally from Tennessee, where her family all live now. Her father died of enlargement of liver, and her mother and six sisters are still living. Two brothers died of pneumonia. Her husband, Q. S., died in 1909 in Oklahoma, of pneumonia. After his death she came to South Carolina and settled in mill village B, where her son, Pellagrin 265, F. S., aged 10 years, developed pellagra in 1910. He had a marked erythema of hands, feet and legs. In 1911 there was a recurrence of erythema and dysentery. Pellagrin 261, the mother, was the next in the family to develop the disease, March, 1911. She was born in 1870, had typhoid many years ago, and malaria three years ago. In March, 1911, she had typical erythema of hands and forearms followed by stomatitis, diarrhea and general weakness. There were no definite symptoms in 1912, but she was not well during the summer. Every year since 1911 she has had diarrhea and weakness. Her mind seems dull; she is listless and stupid. It is difficult to tell whether this is the result of disease or habit.

In April, 1911, three other children, Pellagrins 262, 263 and 264 all developed pellagra. Pellagrin 262, M. S., aged 21 years, had erythema of hands and arms which lasted four months. There was no recurrence in 1912. In 1913 her hands were very red during May and June, but it was attributed to sunburn, although she works in the mill all day. Pellagrin 263, H. S., aged 8 years, had erythema of hands and feet, with severe stomatitis and diarrhea. There was a recurrence in 1912; not present in 1913. Pellagrin 264, M. S., aged 18, had simply erythema of hands and arms without other symptoms. This recurred in 1912, but was not present in 1913. There are four sons and three daughters ranging from 26 years to 4 years, not affected.

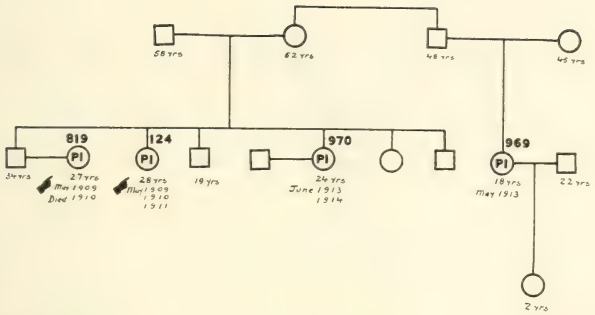


Fig. 7 (T. H. Family).—This family lived in one of the most insanitary mill villages visited. There has been much pellagra there in the last ten years, and there was an outbreak of it in 1909. The father and mother are living, strong and sturdy. They had six children, two of them pellagrins. The wife of one of the sons was also a pellagrin.

Pellagrin 124, O. T., aged 28 years, and her sister-in-law, Pellagrin 819, aged 27 years, developed pellagra about the same time, May, 1909. Pellagrin 819 lost strength rapidly and died in 1910. There were no children. Pellagrin 124, O. T., lived at home, and although she slept with a younger sister, the latter did not contract the disease. She had erythema, stomatitis and later developed diarrhea and dysentery. There were recurrences in May, 1910, and June, 1911, but there has been no recurrence since. In June, 1913, her sister, Pellagrin 970, M. H., also developed the disease. She had married and left home. She had a recurrence in June, 1914. Her cousin, Pellagrin 969, Mrs. J. L., aged 19 years, living near, and next door to a pellagrin, also developed the disease in May, 1913. She has a child 2 years old, not affected.

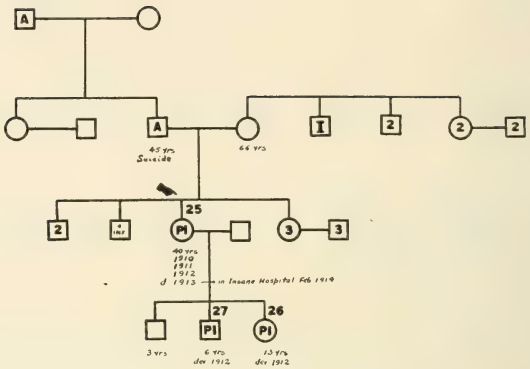


Fig. 8 (G. Family).—Pellagrin 25, J. G., born in 1872 in Georgia, married in 1897. She worked in a mill until 1906; then did housework. In 1908 she had hookworm disease followed by nervous exhaustion and physical debility. She was in the insane hospital when pellagra developed, April, 1910. She recovered sufficiently to go home; had a second attack from May to July, 1911, and a third attack in June, 1912. Her mental condition grew progressively worse, until, after a fourth attack in June, 1913, she was taken to the insane hospital, where she died in February, 1914. She had three children, two of whom were pellagrins. Pellagrin 26, E. G., born in Georgia in 1899, was a healthy child, well developed. In June, 1912, she showed skin and intestinal symptoms of pellagra. Pellagrin 27, C. G., born in 1906 in Georgia, developed pellagra about the same time. These children did not have a recurrence in 1913. They were not seen in 1914. They are now living out of the county. The father of Pellagrin 25 was alcoholic and committed suicide when 45 years of age. The paternal grandfather was also alcoholic. The mother, aged 66, is well and strong and nursed Pellagrin 25 when her mental condition was bad. Two maternal aunts and two maternal uncles are normal. One maternal uncle is insane (manic depressive?). He is in the hospital off and on. They live in Georgia—information meager. None of these relatives are known to have pellagra.

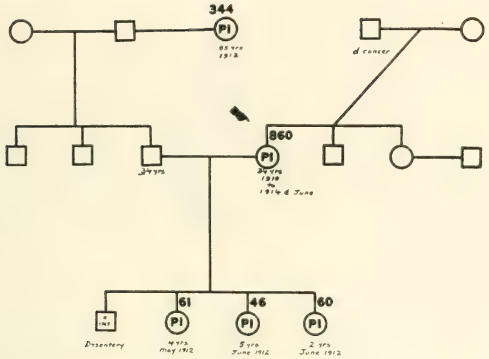


Fig. 9 (Q. Family).—Pellagrin 860, L. Q. S., aged 34 years, was a millworker in S mill village. She developed a typical case of pellagra in 1910, with a slight recurrence each year until June, 1914, when she died. These attacks were not severe enough to interfere with her work at the mill until late in the fall of 1913. Nothing could be learned of her family—she was even reticent concerning her own symptoms. Her husband is living and well. His father died of cancer.

They had four children. One boy died in infancy of dysentery. The three girls are all pellagrins. After they left North Carolina the family came to S mill village into an endemic neighborhood, a severe case of pellagra living three doors away. Pellagrin 61, L. S., aged 4 years, showed first symptoms May 1, 1912. In June of the same year both sisters, Pellagrin 46, aged 6 years, and Pellagrin 60, E. S., aged 8 years, showed typical symptoms. There was no recurrence in 1913 or in 1914.

Late in the summer of 1912 Pellagrin 344, Mrs. A. S., the children's stepgrandmother, who lives with them, developed suspicious symptoms, having severe dysentery and discoloration of skin and peeling. She cared for them while parents were in the mill. In 1913 she was improving and denied having had pellagra.

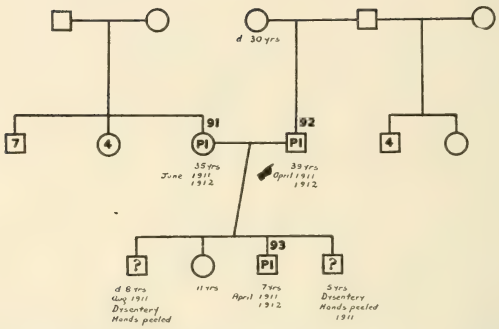


Fig. 10 (Cd. Family).—The Cd. family lived next door to a pellagrin. Mr. J. C., Pellagrin 92, aged 39 years, was a store-keeper from 1909 to 1911 in an endemic center of D mill village. Later he worked in the mill. Late in April, 1911, he developed a well-marked case of pellagra. He had a definite recurrence in 1912. His son, Pellagrin 93, F. C., had developed the disease early in the same month, and he also had a recurrence in 1912. There were three other children. The oldest, a girl 11 years of age, has never shown any symptoms, but both boys are uncertain. A boy, aged 8 years, died in 1911 with dysentery. His hands peeled; and a younger brother, aged 5 years, who is living, also had dysentery and peeling of the hands the same year. These two were reported by the mother in 1912.

The mother took care of the children, and in June she also developed the disease. She had a recurrence in 1912. Her mother, father, seven brothers and four sisters have never shown any symptoms of pellagra.

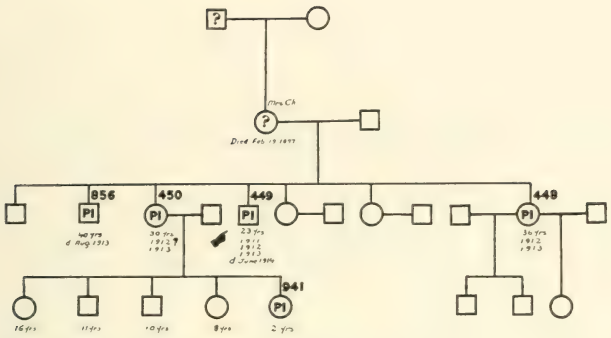


Fig. 11 (Ch. Family).—The maternal grandfather of the Ch. family is said to have died with symptoms resembling pellagra in October, 1896. He lived on a farm in North Carolina, twenty-five miles from his daughter's family. The mother, Mrs. Ch., had recurrent spring attacks of stomatitis, bowel trouble and breaking out of hands and face. Her mind was affected toward the last. She was sick about four years and died Feb. 19, 1897. All the children were living at home while she was sick. Four of them have since developed pellagra. Pellagrin 449, R. C., aged 23, developed pellagra in 1911 or 1912 in Kentucky or North Carolina. In 1913 he visited his sister, Pellagrin 450. He was in a run-down condition, but secured work in the mill and remained with his sister through 1913 and 1914. He grew gradually worse and died in the City Hospital in June, 1914. His sister, Pellagrin 450, aged 30, has had sore mouth and stomatitis for six or seven years. Pellagra was not recognized, however, until 1912. Her hands peeled definitely in 1913. There was no recurrence in 1914.

She has five children, none affected except the youngest, Pellagrin 941, C. C., aged 2 years. She developed gastro-intestinal trouble in January, 1913, and showed her first erythema in May, 1914. She was very fond of her Uncle Bob, Pellagrin 449, and slept with him even after he was confined to bed. They used a common drinking cup. Pellagrin 448, F. D., aged 36, developed pellagra while living in Kentucky in 1912. She later came to a mill village near S; had a recurrence in 1914. Pellagrin 856, H. C., aged 40 years, has had bowel and stomach trouble every spring for three years. He visited in the homes of Pellagrin 448 and Pellagrin 449, staying some nights with one and some with the other. He has been insane since 1912. No erythema was noticed until June, 1913. He died in August, 1913, in North Carolina.

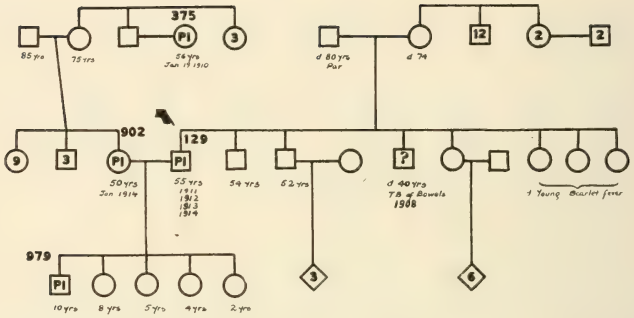


Fig. 12 (T. Family).—Pellagrin 129, aged 55 years, was a farmer in well-to-do circumstances. In 1909 he had a severe attack of typhoid fever, from which he has never fully recovered. In 1911 he developed pellagra, with severe gastro-intestinal symptoms. He has had a recurrence every year since. He became too weak to run his farm and moved to town. His family history is negative, except possibly one brother, who died in 1908 of tuberculosis of the bowels. Pellagrin 902, E. T., aged 50 years, wife of Pellagrin 129, developed a severe attack in 1914. She was taken to the New York Post-Graduate Hospital. She returned during the summer much improved, but still very weak. They have five children, only one of whom has pellagra. This son, Pellagrin 979, R. T., aged 10 years, developed severe erythema with slight intestinal symptoms in July, 1914. He sleeps with his father. The mother and baby sleep together and the three unaffected girls sleep in another room.

Pellagrin 375, D. C. T., aged 56 years, the maternal aunt of Pellagrin 902, developed pellagra in 1909, the same year that Pellagrin 129 had typhoid. She had a severe attack and died Jan. 19, 1910. No history could be obtained of the causes of death of ancestors in either husband's or wife's family. Pellagrin 902 has nine sisters and three brothers living, not affected.

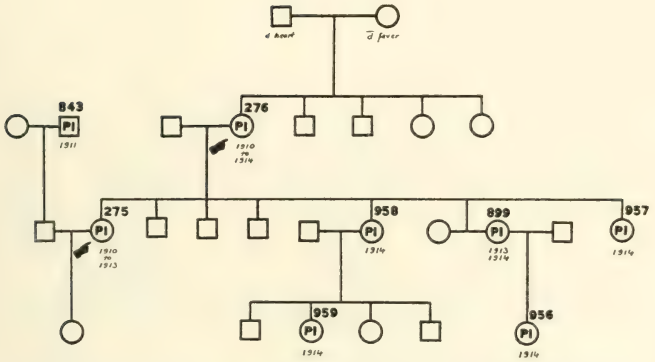


Fig. 13 (W. Family).—In the spring of 1910 Pellagrin 276, Mrs. M. W., and Pellagrin 275, Mrs. E. W., mother and daughter, developed pellagra about the same time. They were both in good physical condition, but Pellagrin 276 gave a history of dysentery in the summer for three years prior to 1910. They had both visited Pellagrins 352 and 825, cases with very severe symptoms. The mother, Pellagrin 276, aged 50 years, had recurrences in 1911, 1912, 1913 and 1914. There has been severe mental disturbance from the beginning of the disease, and when seen in June, 1914, her mind was almost a blank. She was greatly emaciated and a great care to her family. Her ancestors and fraternity are negative to pellagra. Of eight children, four are pellagrins; she has also two pellagrous grandchildren. This family lived in mill village A from 1910 to 1912, when they moved to the country and remained there until June, 1913. They then returned to mill village A and moved into a house just vacated by a pellagrin.

Pellagrin 275, Mrs. E. W., aged 22 years, who developed the disease the same year her mother did, had recurrences in 1911, 1912 and 1913, with a slight return of stomatitis and erythema Aug. 1, 1914. Pellagrin 843, Mr. M. W., father-in-law of Pellagrin 275, was a frequent visitor at his son's house. In 1911 he had a sharp and severe attack of pellagra, but there has been no definite recurrence. In August, 1913, Pellagrin 899, Mrs. W. W. L., another daughter of Pellagrin 276, had all the typical symptoms of pellagra, which recurred with lessened severity in May, 1914. Her daughter, Pellagrin 956, R. L., aged 4 years, developed pellagra in May, 1914. Pellagrin 957, A. W., another daughter of Pellagrin 276, aged 18 years, developed pellagra in February, 1914, and her hands were peeling when Pellagrin 959 developed the disease. Pellagrin 958, Mrs. M. W. P., another married daughter of Pellagrin 276, living next door, aged 23 years, developed the disease in February, 1914, and the gastro-intestinal symptoms were still present in August, 1914. She was a daily visitor at her mother's home. In March, 1914, Pellagrin 959, I. P., daughter of 958, aged 6 years, developed the disease. When seen this child was on the bed by the grandmother, and it is certain that the association was very close in all of these cases.

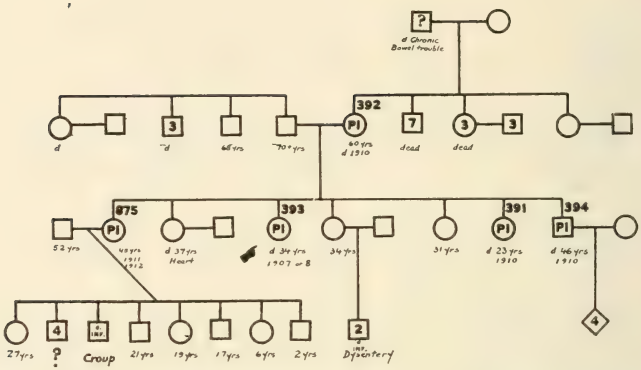


Fig. 14 (H. L. Family).—The first authentic case in the family is Pellagrin 393, M. H., aged 34 years. Hers was one of the early cases of pellagra in Spartanburg County, and she died either in 1907 or 1908. Her mother, Pellagrin 392, A. B. H., aged 60 years, had suffered for several years with chronic bowel trouble and recurrent erythema. She had a stroke of paralysis in 1908. She lost strength rapidly and died in 1910, after being helpless nearly two years. She had seven brothers and three sisters, all dead. None of them were known to have had any signs of pellagra. Her husband, F. A. H., is still living, over 70 years of age. He has one brother living and well. The rest of his family are dead.

There were seven children, four of whom had pellagra. One daughter died at the age of 37 years with heart trouble. One daughter, living and well, lost both her boys in infancy with dysentery. The only son, Pellagrin 394, J. H., aged 40 years, died with pellagra in August, 1910, the same year his mother and sister died. Pellagrin 391, E. H., aged 23 years, died in the State Hospital for the Insane May 15, 1910.

The following year another sister, Pellagrin 875, M. L., aged 45, had severe erythema and gastro-intestinal symptoms, with a recurrence in 1912. Her husband is living and well and there is no history of pellagra in his family. They had six living children ranging in ages from 27 to 2 years, not affected. Five children died in infancy.

It is questionable whether the father of Pellagrin 392 did not die with pellagra. He died with chronic bowel trouble, and the neighbors say he had erythema and mental derangement before death.

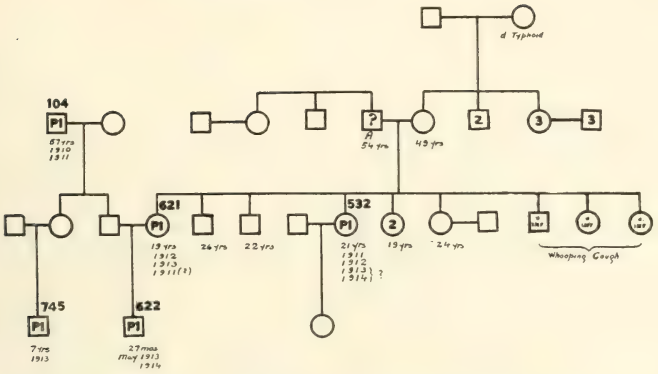


Fig. 15 (P. W. Family).—Pellagrin 104, N. P., aged 57 years, a mill operative, was in good physical condition until the spring of 1910, when he developed a severe case of pellagra. He had severe gastro-intestinal symptoms, stomatitis and erythema. He soon became prostrated and was obliged to give up his work. His wife was afraid that she would contract the disease, so it was necessary for him to visit around among his relatives to get the necessary care. He spent much time with Pellagrin 621, a daughter-in-law, and with his daughter, the mother of Pellagrin 745. He became a little better in the winter, but in the spring of 1911 he had a recurrence. No history of his antecedents was obtainable.

Pellagrin 621, B. P., aged 19 years, waited on her father-in-law in 1910. In 1911 her hands and arms peeled, and it was thought she had pellagra, but no other symptoms developed, and the diagnosis was questionable until 1912, when she had a recurrence with stomatitis and erythema. There was also a recurrence in 1913. In 1914 she was working in the mill, having separated from her husband. She and her son were living at her father's. Her son, Pellagrin 260, H. P., 27 months old, developed pellagra in 1913. When seen in 1914 there was a very slight erythema on the hands and forearms and a slight diarrhea.

In 1911 Pellagrin 532, Mrs. A. B., aged 21 years, sister of Pellagrin 621, developed a well-marked case of pellagra. She lost weight and became apathetic and depressed. She had recurrences in 1912 and 1913, but the symptoms were more mental than physical. She has a daughter not affected. She and her sister visited frequently, and in addition to this, she lived next door to a pellagrin, their water-closets adjoining. Pellagrin 621 and Pellagrin 532 have two brothers and three sisters, never affected. One brother and two sisters died in infancy with whooping-cough. Their father is alcoholic. He is living, aged 54 years, in the country near one of the mill villages in which pellagra is endemic. He had some vague symptoms which the family thought might be pellagra, but the diagnosis was not confirmed. The mother is living and well. Her family, two brothers and three sisters, are negative to pellagra.

Pellagrin 104 has had no recurrence of pellagra since 1911. He still visits around, spending much time with his daughter. Her son, Pellagrin 745, P. C., aged 7 years, is very fond of his grandfather and is with him constantly when opportunity offers. In 1913 he developed a well-defined case of pellagra.

(Query: If pellagra is a germ disease, in what way can it be carried from one person to another? Can a person be a carrier of the disease after he is apparently well?)

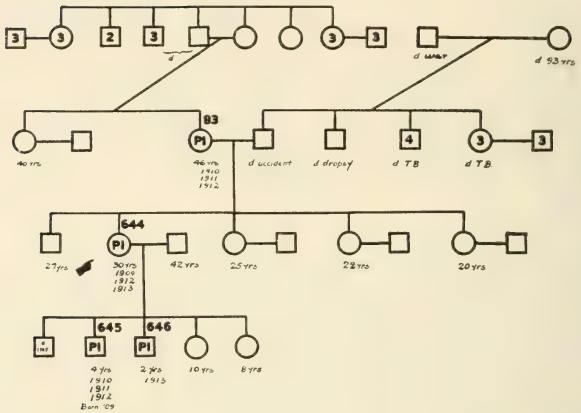


Fig. 16 (F. S. Family).—Pellagrin 83, I. F., 46 years of age, was born in North Carolina. She had typhoid fever twenty-one years ago, since which time her general health has been good. She developed pellagra in June, 1910, while living in W mill village. It recurred in August, 1911, and again in 1912. No details could be obtained of her ancestors except that her father and three uncles died in the war, and the others are living in North Carolina; no history of pellagra in any of them. She has one sister, 40 years of age. Her husband, A. F., died of an accident to his head. His family all died young, one brother with dropsy, four brothers and three sisters with tuberculosis.

Pellagrin 83 had five children ranging in ages from 30 years to 20 years, only one of them having pellagra. Pellagrin 644, A. S., the oldest child, born in North Carolina in 1883, had asthma and heart trouble. She moved to Spartanburg County and the first symptom of pellagra appeared in April, 1909. It was quite mild, as she was four months pregnant. Her baby was born in September, 1909. Her second attack was in 1910, but there was no erythema on the hands. The third attack occurred in 1911, but without erythema on hands; fourth attack occurred in 1912 with stomatitis; fifth attack, in 1913, mild, but with definite and typical eruption. She has lost 22 pounds in two years. She has had five children: One son died in infancy, two daughters are well, and two children born while she had pellagra have both developed the disease.

Pellagrin 645, F. S., born in September, 1909, developed pellagra in March, 1910, and has had recurrences in 1911, 1912 and 1913. Pellagrin 646, A. S., born in September, 1911, developed the disease in 1913. These children have had slight attacks of erythema with rather severe intestinal symptoms.

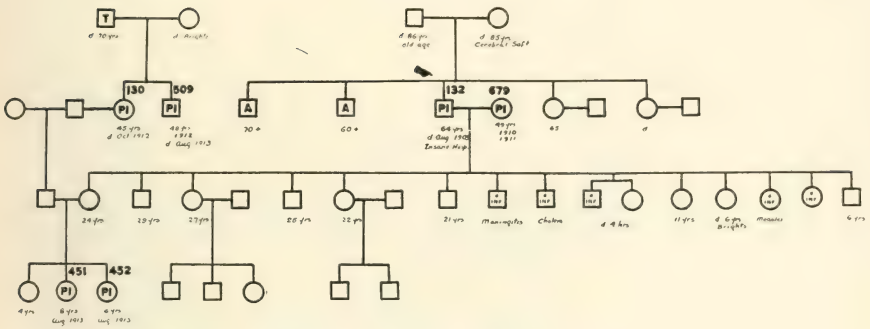


Fig. 17 (S. B. Family).—The S. B. family history is offered to show the way pellagra seems to be transmitted to others by close association. The earliest known case in this family was Pellagrin 132, Mr. J. B., aged 64 years. He was naturally a strong man, slightly but not excessively alcoholic. His digestion had been impaired for several years. He was a mill worker in mill village S and lived in an endemic area. He developed pellagra in the spring of 1909. He had marked erythema, severe diarrhea and decided mental disturbance. He grew rapidly worse and was taken to the State Hospital for the Insane, where he died in August, 1909. His wife denies that he had pellagra. She says that he had sunburn and died of cerebral softening just as his mother did. Two of his brothers, both alcoholic, are living; one sister is living, and one died a few years ago. None of them showed any pellagra symptoms. They did not live in the same section.

His wife, Pellagrin 679, Mrs. J. B., aged 49 years, took care of her husband until he went to the hospital. The next spring, 1910, she had a slight attack of pellagra without mental symptoms. She had also a recurrence in 1911. It was impossible to get her family history, as she resented questioning and even denied the presence of pellagra in herself and husband. They had fifteen children: six died in infancy, one died of Bright's disease when 6 years of age; the other eight are all living, none of them ever having shown signs of pellagra, although six of them lived at home when the mother and father had pellagra.

Two grandchildren, Pellagrin 451, A. S., aged 8 years, and Pellagrin 452, P. S., aged 6 years, developed pellagra in August, 1913. A younger sister in the same household is free from the disease. In addition to living in an endemic section and playing with affected children, these children were frequent visitors at the home of their step-grandmother, who died of pellagra the previous year. Pellagrin 130, Mrs. P. S., aged 45 years, the step-grandmother mentioned, was always visiting the sick and waiting on them. She developed pellagra in 1911 or 1912. She had very severe erythema and intestinal trouble and died in October, 1912. Her brother, Pellagrin 509, J. S., aged 48 years, visited at the home of his sister, staying over night and often eating there. In 1912 he developed pellagra, and in August, 1913, he died at the Pellagra Hospital. His skin lesions were very severe and diarrhea excessive.

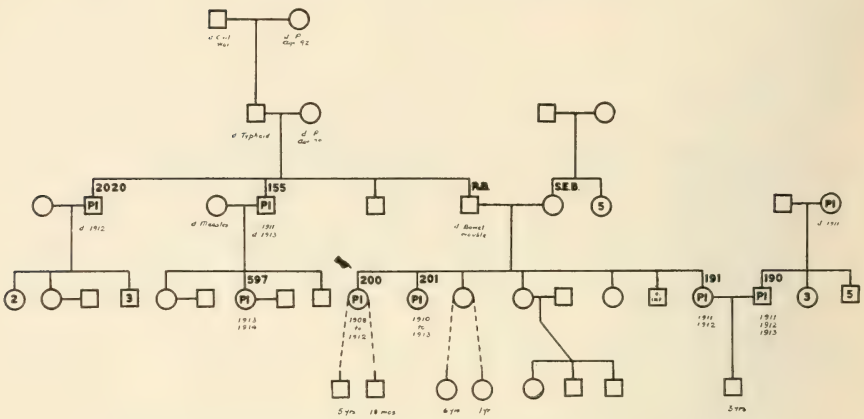


Fig. 18 (B. Family).—The first member of the B. family to show symptoms was Pellagrin 200, M. B., aged 30 years. In 1906 she had typhoid fever; the following year she gave birth to an illegitimate child. She did not fully recover, had dysentery off and on, and early in 1908 developed pellagra. There were five recurrences. Her health has been improving since 1912. In 1911 she gave birth to another illegitimate child. Her sister, Pellagrin 201, developed pellagra in May, 1910, and had recurrences in 1911, 1912 and 1913. Another sister, Pellagrin 191, Mrs. J. T., had a well-defined attack in 1911, with slight recurrence in 1912. Pellagrin 190, husband of Pellagrin 191, also developed pellagra in 1911. Symptoms subsided partially with cold weather, and there has been a recurrence of erythema every year, but less severe; the nervous symptoms were increasing in 1913. He was not seen in 1914. They have a son 3 years old, not affected. This family were frequent visitors at the home of Pellagrins 200 and 201. The mother of Pellagrin 190 is said to have died in 1911 of pellagra. His father, three sisters and five brothers are negative to the disease. Two other sisters of Pellagrin 200, living at home, have never shown any symptoms. The mother, S. E. B., still living in S, aged 60, has never shown any symptoms. Her father, mother and five sisters are negative to pellagra.

The father, R. B., died twenty years ago, aged 41, with chronic bowel trouble which lasted fourteen months. The father's brother, Pellagrin 155, G. B., aged 55 years, developed pellagra in 1911. He had typhoid when 10 years of age. He was poorly nourished and anemic, a frequent visitor at the homes of Pellagrins 200 and 201, and lived in endemic section of mill village A. In 1912 there was no definite recurrence. Early in the spring of 1913 he had a severe recurrent attack, which resulted in death in August, 1913. His daughter, Pellagrin 597, V. Q., nursed him until he was taken to the hospital. She had typhoid fever in 1909 and married in April, 1912. She continued to work in the mill until April, 1913, and lost 40 pounds in weight during the year. In May, 1913, pellagra developed. She had a very mild recurrence in 1914. One sister not living at home and four brothers living at home did not develop the disease.

Her paternal grandfather, W. B., died of typhoid fever. Her paternal grandmother, S. H. B., died of paralysis, aged 78. The paternal great-grandfather, W. B., died in the Civil War. The paternal great-grandmother, S. J., died of paralysis, aged 92 years.

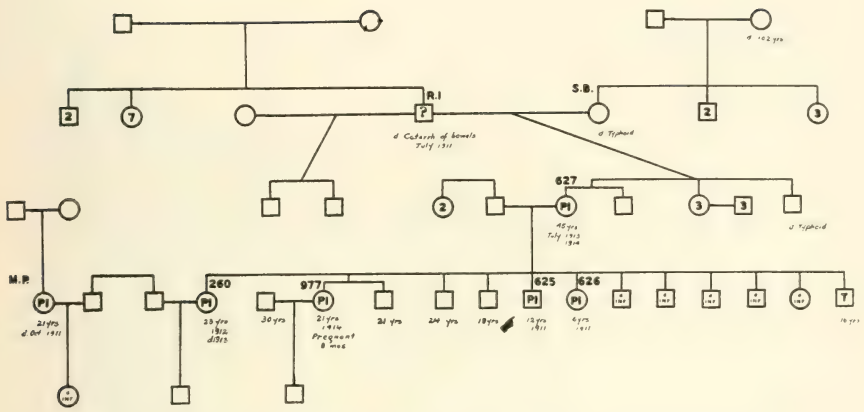


Fig. 19 (R. Family).—Pellagrin 260, S. M. P., aged 23 years, had the first case of pellagra discovered in this family. She developed it during pregnancy in 1912. She lived with her mother until the mental symptoms became marked, when she was taken to the Good Samaritan Hospital, where she died on Sept. 7, 1913. In July, 1913, the mother, Pellagrin 627, M. E. R., aged 45 years, had typical symptoms. She has eight living children. Four sons have shown no symptoms of pellagra. One son, 16 years of age, has a pronounced case of tuberculosis. There were five children who died in infancy, either being born dead or having died in a few days or hours. Two sons, D. R., Pellagrin 625, aged 12 years, and P. R., Pellagrin 626, aged 6 years, had pronounced symptoms in 1911, the same year her father died with catarrh of the bowels. In June, 1914, M. L., Pellagrin 977, visited her mother for a week. The mother returned home with her and spent two weeks. July 6, 1914, Pellagrin 977 developed the disease. As she was eight months pregnant, she was quite nervous for fear she would have it as Pellagrin 260 did.

Mrs. R., Pellagrin 627, could not remember whether her father, R. L., had skin symptoms or not. He died of catarrh of the bowels in July, 1911. He had seven sisters and two brothers, who were negative to pellagra. R. L. was married twice. By his second wife there were two sons, living and well; by his first wife there were six children. One son, B. L., died of typhoid; one daughter, Pellagrin 627, mother of Pellagrin 260, has pellagra; the others are living in South Carolina and are well. The maternal grandmother, S. B., died of typhoid. The history of her two brothers and three sisters is unknown. Her mother died at the age of 102, of old age. M. P., a sister-in-law of Pellagrin 260, living diagonally across the street from the R. family, died of pellagra in October, 1911.

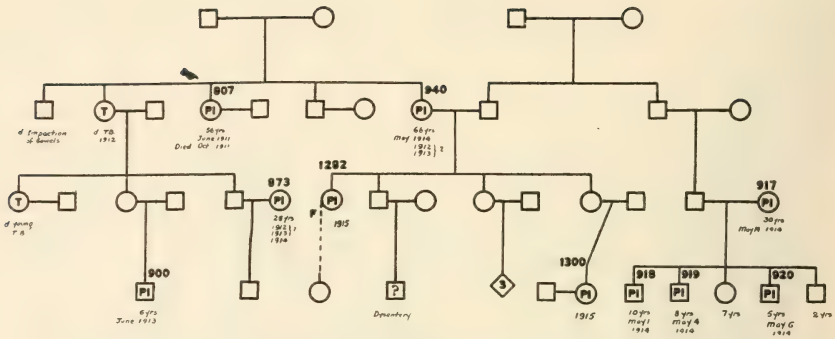


Fig. 20 (H. Family).—The pellagrins in this group are all related, but they represent three distinct families. Pellagrins 873 and 917 married into the H. family. They were, however, so intimately connected that it was impossible to consider them separately. The first member of the H. family to develop pellagra was Pellagrin 807, Mrs. F. H. M., aged 56 years. She was living in the country and no contact history could be obtained, but it is known that four other cases within a radius of one mile developed pellagra the same year. Pellagrin 807 began April, 1910, to show symptoms of indigestion followed by bowel trouble. She was sick during the summer, but in December was feeling much better. In February, 1911, she had a very severe attack of indigestion, lost weight, and in June, 1911, developed erythema on the hands and arms. She died on Oct. 11, 1911. She was cared for by her nephew's wife, Pellagrin 873. Later she was taken to her sister's, Pellagrin 940, in village A, where she died in about ten days.

Pellagrin 873, Mrs. F. H. C., niece by marriage, lived nearly opposite Pellagrin 807, and nursed her for several months. She had indefinite symptoms of pellagra in 1912 and again in 1913, insomnia, burning of the hands, weakness and dizzy feelings. The first erythema appeared in April, 1914. She now has a well-developed case of pellagra. Her husband's sister died in 1912 of tuberculosis. Another sister of the husband lives only 100 yards away, and the son of this woman, Pellagrin 900, H. C., aged 6 years, developed pellagra in June, 1913, with recurrence in June, 1914. There was a typical eruption each year. He was a constant visitor at the house of Pellagrin 873.

Pellagrin 940, F. H. B., aged 66, at whose home Pellagrin 807 died, has had indigestion and loose bowels since 1912. In May, 1914, the first erythema appeared, accompanied by weakness, loose bowels and stomatitis. When last seen, Aug. 1, 1914, she was in bed with weakness and mental symptoms. One brother of Pellagrin 940 is still living. One sister died of tuberculosis and one brother died last year of impaction of the bowels.

Pellagrin 1282, L. B., aged 29 years, living with her mother, Pellagrin 940, developed pellagra in June, 1915; other early symptoms were denied. There was slight desquamation still present when seen Aug. 6, 1915. Pellagrin 1300, M. P. W., aged 22 years, granddaughter of Pellagrin 940, developed pellagra in July, 1915, while in Danville, Va. She had been living there only three months when the disease developed. Prior to that time she had lived in mill village Sa, next door to a pellagrin, whose son she married.

Pellagrin 917, Mrs. S. B., aged 30 years, niece by marriage, lived near her aunt in an endemic area five months before pellagra developed. She had lived four years prior to this next door to a pellagrin; there was very intimate association, and the children played together. She and three of her four children, Pellagrins 918, 919 and 920, all developed definite cases in May, 1914. Pellagrin 918, A. B., the 10-year-old son, was the first to show symptoms, the others following in quick succession.

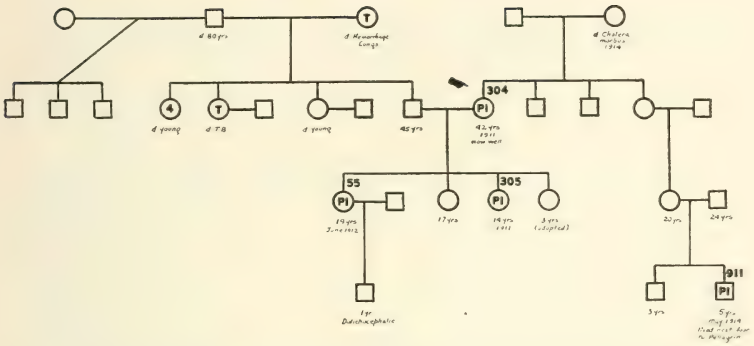


Fig. 21 (P. Family).—The maternal grandmother died in 1904 with cholera morbus. The father's family was tubercular. The mother, Pellagrin 304, Mrs. J. P., aged 42 years, developed pellagra in mill village S, an endemic center. She had no recurrence in 1912 and 1913. Her daughter, Pellagrin 305, Miss O. P., aged 14, had active symptoms the same year. Another daughter, Mrs. G. P. G., Pellagrin 55, aged 19, moved in March, 1912, to a house in the country formerly occupied by Pellagrin 56. In June, 1912, she developed pellagra. She had been closely associated with her mother and sister, and had lived in several mill villages where pellagra existed. When seen in 1913 there were no active symptoms, but she was very weak and had digestive trouble; was pregnant. Her son, 1 year old, has had chronic bowel trouble all his life. He is dolichocephalic.

In May, 1914, Pellagrin 911, J. B., aged 5 years, the son of a cousin of Pellagrin 55, developed pellagra. The family had been living from December, 1913, to February, 1914 in a house next door to Pellagrin 133.

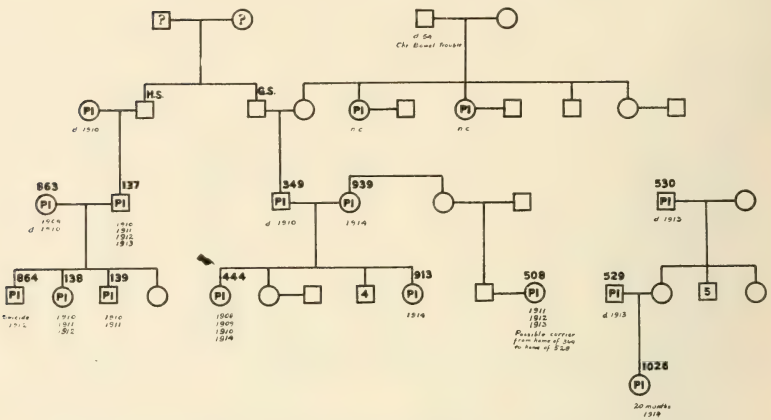


Fig. 22 (S. Family).—The paternal grandfather of Pellagrin 137 and Pellagrin 349 lived and died in Spartanburg County; cause of death unknown. He had two sons, H. S. and G. S. H. S. married M. C., who died in 1910 with pellagra. She had not been well for two years prior to the development of the disease. Their son, Pellagrin 137, Mr. J. S., developed pellagra the year his mother died. At that time he was living on a farm not in an endemic section, but visited his mother frequently, and she also paid long visits to him. In 1907 he began to have chronic dysentery and indigestion, and in 1908 had a severe and prolonged attack of malaria. His digestion became more impaired and in 1910 he had typical erythema accompanied by gastro-intestinal symptoms and mental disturbance. In June he went to the Columbia State Hospital for treatment and remained there six weeks. Symptoms subsided and he returned home. There were recurrences in 1911, 1912 and very slightly in 1913. His wife, Pellagrin 863, Mrs. J. S., developed pellagra in the fall of 1909. She had a very severe attack and died in April, 1910. There were four children.

Pellagrin 864, C. S., son, developed pellagra in 1911 and in 1912 developed marked mental symptoms. He tried to shoot his wife and was taken to the Columbia State Hospital, where he committed suicide. Pellagrin 138, A. L. S., daughter aged 17 years, had erythema in 1910, with recurrences in 1911 and 1912. There were no symptoms in 1913. Pellagrin 139, C. S., son aged 19 years, developed pellagra in 1910, with recurrences in 1911. There were no definite symptoms in 1912 and 1913. One daughter, 15 years of age, living in the same house, did not have the disease.

G. S., the other son, married and had a son, Pellagrin 349, G. S., aged 53 years, who developed pellagra in the spring of 1909 after caring for his daughter, Pellagrin 444. There is no history of contact with his cousin's family. Pellagrin 444, C. S., aged 10 years, developed pellagra in the spring of 1908. It recurred in 1909 and 1910. The erythema was severe, especially on the feet and legs. These were dressed by his father, Pellagrin 349, who developed the disease and died in June, 1910. Pellagrin 444, had no recurrences of the disease after 1910 until May, 1914. In June, 1914, her sister, Pellagrin 913, L. S., aged 6 years, developed it. Four brothers and one married sister living at home have not yet had the disease. In June, 1914, the mother, Pellagrin 939, Mrs. G. S., aged 42 years, developed a well-marked attack of pellagra. Their home is in an endemic section. The question arises whether there was a fresh infection in 1914, or whether Pellagrin 444 had a recurrence after three years.

It was impossible to get the history of this family on the paternal side. The maternal grandfather of Pellagrin 349 died with chronic bowel trouble. Two aunts died with pellagra.

There is an interesting connecting-link between this family and the E. family. Pellagrin 508, E. C., aged 20, lived with the family of Pellagrin 349 for one year, 1910. In 1911 she developed pellagra. She boarded with Mr. H. L., Pellagrin 529, in 1912, when she had a recurrence. From there she went to North Carolina, where she remained six months. In the spring of 1913 she returned, married a nephew of Pellagrin 939 and boarded in the vicinity, being a frequent visitor at the homes of Pellagrin 939 and Pellagrin 529. She died in May, 1913.

Pellagrin 529, with whom Pellagrin 508 boarded, Mr. H. L., aged 23, developed pellagra in March, 1913. His mental symptoms were marked from the first. He went to Tennessee, where he died in the summer of 1913. Before going to Tennessee he lived eleven weeks with his wife and baby in rooms upstairs in the home of his father-in-law, Pellagrin 530, Mr. E., who developed pellagra in May, 1913. He became rapidly worse, lost weight, and died in July, 1913. In July, 1914, T. L., daughter of Pellagrin 529, and granddaughter of Pellagrin 530 developed a typical case of pellagra, Case 1026.

This chart seems to signify heredity, but it will be noticed that there are five distinct families represented by pellagrins, and in every instance except the case of the mother of Pellagrin 137 and the case of Pellagrin 444 there is a history of close contact.

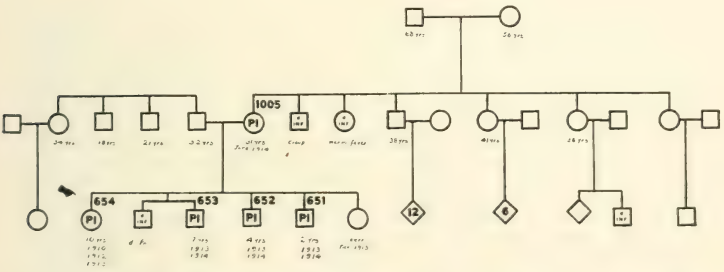


Fig. 23 (F. Family).—The first member of the F. family to develop pellagra was Pellagrin 654, B. F., aged 10 years, a school girl. She had typhoid when 2 years of age, but recovered and was apparently in good physical condition in 1910, when the first symptoms appeared. There were recurrences in 1912 and 1913, but in 1914 she seemed perfectly well. In June, 1913, the three remaining children, Pellagrin 653, P. F., aged 7 years, Pellagrin 652, C. F., aged 4 years, and Pellagrin 651, T. C. F., aged 2 years, all had severe bowel trouble and showed the typical skin lesions. Each of these three children had a recurrence in May, 1914. R. F., born November, 1913, had not developed pellagra.

Pellagrin 1005, N. P. F., the mother, also has the disease. She developed it in June, 1914. There is no known physical defect in her family. Her father and mother are living and well, and she has two brothers, three sisters and twenty nieces and nephews, who have never had pellagra. One brother died in infancy of "worm-fever." She lost one son, the twin brother of Pellagrin 653, when 21 months old, with pneumonia.

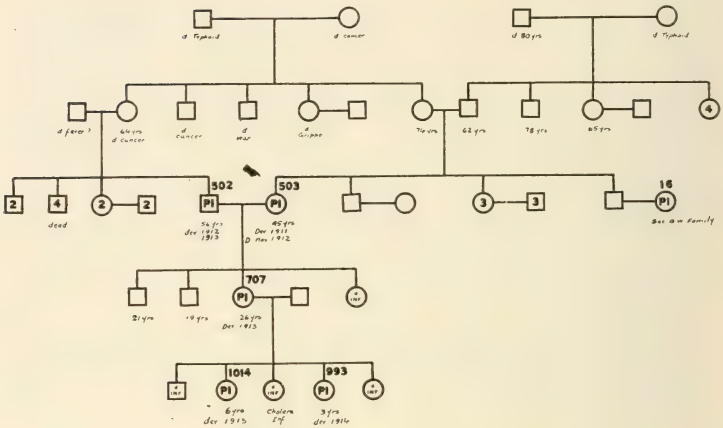


Fig. 24 (B. R. Family).—The first member of this family to have pellagra was Pellagrin 503, although her brother's wife, Pellagrin 16, had it three years earlier. It is not known whether there was close association or not. Pellagrin 503, F. B. R., aged 45 years, was always a hard worker at housework exclusively. She developed pellagra in May or June, 1911; she seemed to get better during the winter, but had a recurrence in 1912, with marked mental symptoms. She died in November. She visited frequently Pellagrin 110. Her husband, Pellagrin 502, W. R., aged 56, born on a farm near Columbia in 1857, was a farmer all his life. His general health was good. In 1912 he began to have trouble with his digestion, and early in November, 1912, he developed typical symptoms of pellagra. These recurred in 1913, but in 1914 there were no marked symptoms though there was a general weakness. In addition to living with his wife, he was a frequent visitor at the homes of Pellagrins 110, 130 and 17. They had four children: one died in infancy; two sons were not affected, and a daughter, Pellagrin 707, M. C., 26 years of age, who had a typical attack of pellagra in the summer of 1913, was a constant visitor at her mother's home and after the mother's death lived with her father. She is married and has had five children. Three died in infancy, one with cholera infantum and one teething. Two are pellagrins. Pellagrin 1014, M. C., 6 years of age, developed the disease in 1913. She lived most of the time with her grandmother, often sleeping with her. Pellagrin 993, K. C., aged 3 years, developed pellagra in 1914. Hygiene and sanitation were practically unknown in this family.

The mothers of Pellagrin 502 and Pellagrin 503 were sisters. The mother of Pellagrin 502 died with cancer; her brother and mother died with the same disease. The mother of Pellagrin 503 is still living, aged 74 years, strong and healthy. The father of Pellagrin 503 is also living. They are better-class mill people, and are in very comfortable circumstances. The father's mother and the mother's father died of typhoid.

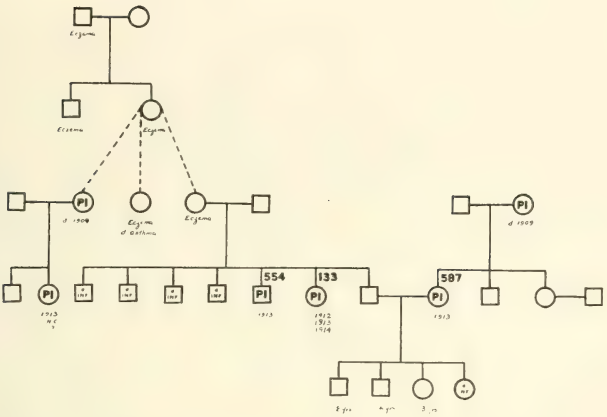


Fig. 25 (C. Family).—The C. family has had eczema as far back as its history can be traced. The maternal grandfather had indigestion and eczema. The mother and uncle both had eczema so badly that the hands had to be wrapped in winter. The mother had three illegitimate children; one, C. B., died in 1904, with all symptoms of pellagra. Her hands and feet were badly broken out and marked gastro-intestinal symptoms and severe mental disturbance occurred before death. Her daughter is said to have developed pellagra in 1913, but as she lives in North Carolina, this report was not verified. One daughter died at the age of 33, with asthma. The other daughter, mother of Pellagrins 133 and 554, has had eczema all her life. The family is living in mill village S in abject poverty. Hygiene, personal and domestic, is unknown. The diet is poor in quality and insufficient in quantity.

In 1910 the family lived in mill village I in a house formerly occupied by a pellagrin. In March, 1912, they moved to S, into a house formerly occupied by Pellagrins 17 and 402. In May, Pellagrin 133, D. C., developed pellagra. She had recurrences in 1913 and 1914. Her brother, Pellagrin 554, W. C., living in the same house, developed pellagra in 1913. He has been in poor health for years. Pellagrin 587, L. C., sister-in-law of Pellagrin 133, visited this house many times, staying night and day. In April, 1913, while here on a visit, she developed pellagra. Erythema was very severe and mental symptoms marked. Three children who accompanied her on the visit have not developed the disease. Her mother, N. S. P., had catarrh of the bowels for years, and in 1909 died with all the symptoms of pellagra. She was cared for by Pellagrin 587.

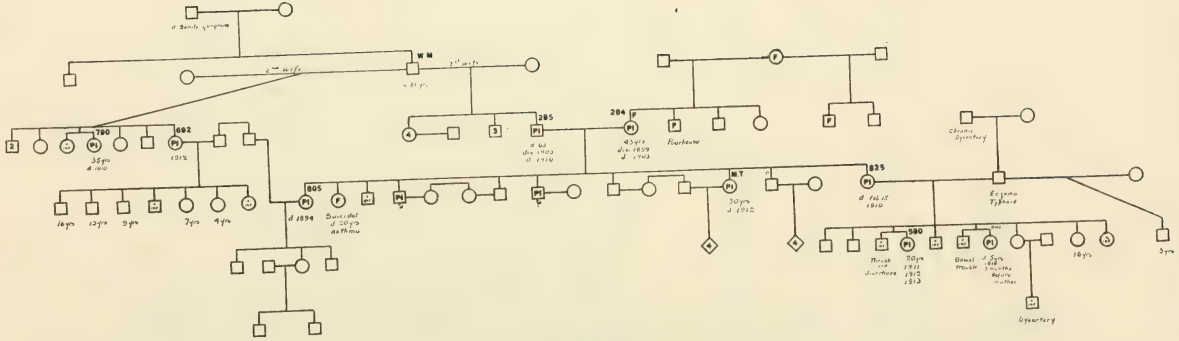


Figure 26.

Fig. 26 (M. Family).—In 1893 Pellagrin 805 went with her husband to the farm of her uncle, where Italian laborers were employed to help with the farmwork. They stayed there during May, June and July, 1893, when they returned home. In the spring of 1894 Pellagrin 805 developed pellagra and died in October of the same year. This was one of the earliest-known cases of pellagra in Spartanburg County. In her fraternity there were ten children. One sister, J. M., was feebleminded. She had asthma after second year of life. Her mental condition became so marked that she was taken to Columbia Hospital in 1906, where she remained six years. She was suicidal at times. She died at Columbia Hospital in 1912. One brother died at birth. Five brothers are living in various parts of South Carolina and North Carolina. It is reported that two of the brothers are pellagrins, but this has not been verified. One sister, M. T., aged 30 years, died in 1912, of pellagra. Her husband and four children are not affected. One sister, Pellagrin 825, died in 1910 at A. She was very badly affected, and not having any one of the family able to care for her, she was nursed at intervals by various friends and neighbors. She died in 1910. (It is worthy of note that many new cases of pellagra developed in this mill village the following year.) The house was thoroughly fumigated after her death. Her husband has married a second time and has a son aged 3 years. The family are still living in the village. He was the father of ten children by Pellagrin 825.

Two daughters and two sons of this couple are living at home unaffected. One son died at 18 months with thrush and diarrhea. One girl, a twin, died in 1910, three months before her mother, aged 5 years, 7 months. She had erythema, severe bowel trouble, and was "crazy" for six weeks before death. Another baby girl died at birth. One daughter, aged 19, married. She is not affected. Her son died, aged 20 months, of dysentery. She has no other children. Another daughter, Pellagrin 580, who married in 1910, developed pellagra in July, 1911, and has had recurrences in 1912, 1913 and 1914. She had severe mental symptoms in 1913, with stomatitis and bowel trouble. There was a remission during the winter, but early in January there was severe recurrence. She is at present anemic, listless and indifferent to her surroundings. The parental grandmother of Pellagrin 580 had chronic dysentery for years, and her father has eczema, which developed after an attack of typhoid.

The maternal grandmother, Pellagrin 284, a woman of weak intellect, whose mother and two brothers were feebleminded, developed pellagra in 1899 in A, Spartanburg County, and later moved to S, where she died in June, 1903. Mental symptoms were pronounced for three months before death. The maternal grandfather, Pellagrin 285, developed pellagra at S in 1903. He died at his son's home in Laurens County in 1910. There was complete mental failure before death. He was the only one of seven children known to have pellagra. His father, W. M., lived and died in Laurens County. He was always strong and healthy, and died of old age, 81 years. The brother of W. M. died in the southern part of Spartanburg County, aged 80 years. Their father died of gangrene. W. M. was married twice. His widow is living in E, Spartanburg County. By his second wife there were six children, all living except twin girls. One died in infancy, the other, Pellagrin 790, N. M., died at E, in Spartanburg County in 1910, of pellagra. Her mental symptoms were marked. Another daughter, Pellagrin 692, was reported to have pellagra in 1912. There was no recurrence in 1913 or 1914.

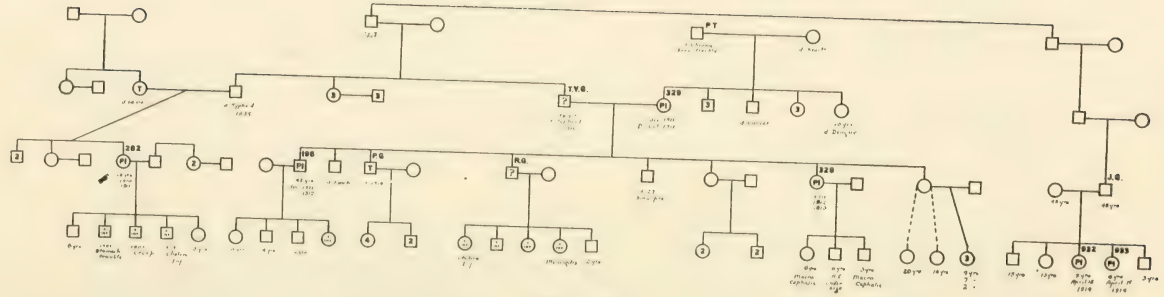


Figure 27.

Fig. 27 (T. G. Family).—P. T., the maternal grandfather of Pellagrin 198, died of "chronic bowel trouble." His wife died with heart trouble. Pellagrin 329, N. T., the mother of Pellagrin 198, died of pellagra in October, 1911. She developed it in the early spring. She had the usual skin and intestinal symptoms; her mind soon became affected and she needed constant watching. Her son, Pellagrin 198, spent much time at her house and took care of her at night. Her husband, T. V. G., had died the previous year of typhoid fever. He had chronic bowel trouble for six months, ten years before death, without any recurrence. Pellagrin 329 had serious bowel trouble at the same time, and three years before death, that is, in 1908, she had another attack. T. V. G. had three sisters, whose families are free from pellagra. One brother died in 1895 with typhoid fever. This brother's wife died, aged 66 years, of tuberculosis. They had four children, one of whom, Pellagrin 282, J. C., aged 28 years, developed pellagra in 1910 and had a recurrence in 1911. There has been no known recurrence since, and it was not ascertained whether there was association between the families the year that T. V. C. had typhoid. Pellagrin 282 had five children: three died in infancy before their mother had pellagra, and two, the oldest and the youngest, are living, free from the disease. The youngest was one year old when the mother developed the disease.

Pellagrin 198, T. G., aged 42 years, developed pellagra in 1911, the year his mother died. Erythema appeared on arms, hands and neck. Later, stomatitis and diarrhea occurred. There was a recurrence of symptoms in 1912, but when seen in 1913 and 1914 the patient seemed to have recovered. He has three children, all well; one child died in infancy. One brother of Pellagrin 198 died of heart trouble. One brother, P. G., died of tuberculosis in June, 1914. Six children and his wife are well. Unusual precautions were taken by his wife to prevent infection. One brother, R. G., has had indefinite symptoms of pellagra for four years. He lives near Pellagrin 198, and their families are closely associated. He married a strong woman, but out of five children, only one, a boy 17 months old, is living. One daughter died of cholera infantum, one of whooping-cough, one of meningitis, and one son was born dead. One sister of Pellagrin 198, B. M., Pellagrin 328, developed pellagra in 1911. She had a recurrence in 1912 and in 1913. She has three children, one of whom, M. M., 8 years of age, is macrocephalic. She was "born with bowel trouble" and did not walk for three years. She has never been to school. She is affectionate, but mentally dull and sluggish in movements. F. M., 6 years old, is undersize and has a harelip. G. M., 3 years old, is macrocephalic, and does not walk yet. One sister of Pellagrin 198, L. T., had two illegitimate children. She is now married to an old man and has three other girls. All seem normal.

In April, 1914, Pellagrins 932 and 933, two children of J. G., a second cousin of Pellagrin 198, developed pellagra in mill village P. There has been no association with the other members of the family for years. A family of children living directly across the street from Pellagrins 932 and 933 developed pellagra in 1913 and the children all play together. Two other children, aged 15 years and 13 years respectively, working in the mill, and the baby, aged 3 years, were free from the disease.

(Query: Have these children an inherited weakness, making them more susceptible than a dozen other children who are playmates of these same pellagrins?)

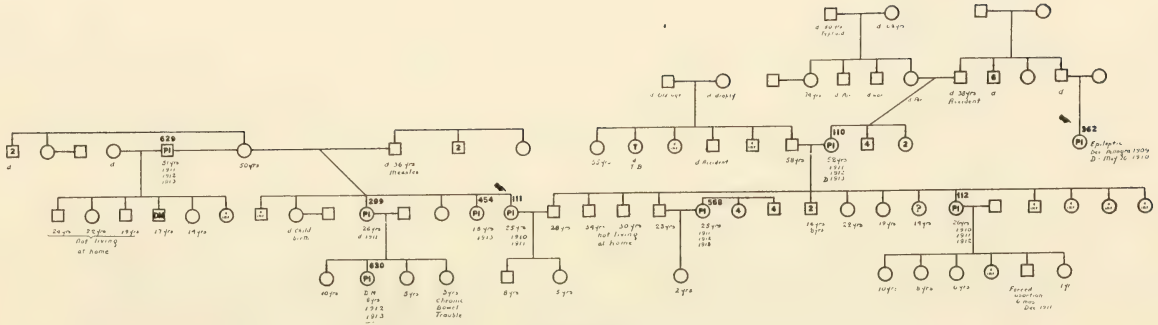


Figure 28.

Fig. 28 (H. W. Family).—The members of this family lived in two mill villages where pellagra was endemic. They were poor, ignorant, unclean and degenerate. Conditions in the homes were as bad, if not worse, than in any of the homes visited. This, in spite of the fact that there were several mill workers whose wages, if pooled, would make a larger income than is common in the South.

Pellagrin 110, Mrs. M. H., aged 52 years, visited many of the pellagrins in S mill village and helped to "lay out" several after death. She developed the disease in a very severe form in July, 1911. She had a recurrence in 1912, followed by progressive weakness until her death in 1913. She had four brothers and two sisters, still living and unaffected. Her mother and maternal uncle died of paralysis and her maternal grandfather of typhoid. Her father was accidentally killed when a young man. His family history is very vague, most of his fraternity being dead. He had a niece, Pellagrin 362, A. H., an epileptic, who developed pellagra in December, 1909, in S mill village and died in June, 1910. Nothing definite could be learned of this case except that her symptoms were severe and she was visited by many of the village people. An epidemic of pellagra in S mill village in 1910 and 1911 may or may not have originated here.

Pellagrin 110 married a man who is still living and whose family history is negative to pellagra. One of his brothers was accidentally shot, one died in infancy and one sister died also in infancy; one sister died young of tuberculosis, and one sister is still living and is well. This couple had fourteen children, only one of whom developed pellagra, Pellagrin 112. The wives of two of the sons, Pellagrin 111 and Pellagrin 568, however, developed pellagra. Of the fourteen children, four died in infancy.

Pellagrin 112, Mrs. M. N., aged 26 years, developed pellagra in 1910 and has had recurrences every year since, except in 1914. She lived in the country about a mile from her mother's home. In 1911, owing to persistent vomiting, there was an induced abortion of a 6 months' child. In 1913 a child was born who showed no symptoms of pellagra. There are three older children, aged from 10 to 6 years.

Pellagrin 568, L. H., aged 25 years, married B. H., son of Pellagrin 110. Her father, mother, four sisters and four brothers are living in North Carolina and they have never seen a case of pellagra. She developed the disease in 1911 and had recurrences in 1912 and 1913. A son, born after she developed pellagra, has no symptoms.

Pellagrin 111, Mrs. F. H., aged 25 years, has lived part of the time with Pellagrin 110 and part of the time she has kept house herself. She was a constant visitor at the homes of pellagrins. She developed the disease in 1910. There was a slight recurrence in 1911, but there have been no symptoms since. She has two children, aged 8 years and 5 years, who show no symptoms of pellagra. In her family there are three other cases of pellagra. Her sister, Pellagrin 299, P. D., aged 26 years, living in P mill village, died in 1911 of the disease. She left four children, one a deaf-mute, Pellagrin 630, G. D., aged 6 years, who developed pellagra in 1912, and had a recurrence in 1913. The youngest child has had chronic bowel trouble for three years. No definite history of erythema could be obtained. Pellagrin 454, A. W., aged 18 years, another sister, developed pellagra in 1913. Her stepfather, Pellagrin 629, developed pellagra in 1911. He worked in the mill until this time. He had a recurrence in 1912 and most decided symptoms in 1913, when he was in the hospital for months. He has a deaf-mute son, aged 17 years; also a daughter, aged 14 years, by a former wife. He also has three sons not living with him, none showing any pellagra symptoms.

STUDIES IN CEREBRAL FAT EMBOLISM

WITH REFERENCE TO THE PATHOLOGY OF DELIRIUM AND COMA *

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INTRODUCTORY

In a previous study[1] of the tissues of fourteen persons who died following fractures complicated by fat embolism, an attempt was made to correlate the amount of fat present in the blood vessels of the various organs, demonstrable by histologic methods, with the severity of the symptoms noted clinically and the frequency with which the delirium occurring after fractures was ascribed to alcoholism was emphasized. In eight of the fourteen, delirium tremens had been diagnosed clinically, although histories of alcoholism had not been definitely established in each of the cases. The study was made on the bodies coming to necropsy from the Cook County and Presbyterian hospitals, Chicago. One of these, which will be called Case A, because of the pronounced clinical manifestations and marked anatomic changes was chosen as the standard.

Preparation of the tissues for purpose of accurate estimation of the fat content was as follows: The tissues were embedded in a 10 per cent. gelatin solution, hardened in formaldehyd vapor at 37 C. for seventy-two hours, or until they were sufficiently hard to permit cutting with the usual sliding microtome, stained with sudan III, and counterstained with hematoxylin, then mounted in glycerol. This method is discussed in the previous report. It has the advantage of keeping the fat globules in their vascular beds, preventing their loss or displacement in cutting, and the counterstain enables a simultaneous histologic study. Sections so embedded were cut to from 5 to 15 microns without loss of the fat globules. Of each piece of tissue, fifty sections were examined; and of these, five sections containing average amounts of fat emboli were set aside for comparison. When these were collected they were carefully examined, and the amount of fat in ten fields of each organ was compared to the amount in ten fields of the same organ of Case A, which was regarded as containing 100 per cent. Then the percentages of fat emboli in the sev-

* Submitted for publication Feb. 24, 1916.

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1. LeCount and Gauss: A Study of Fat Embolism Associated with Fractures, Tr. Chicago Path. Soc., 1915, ix, 251.

eral organs of each body were averaged and compared to Case A. The result was that the other thirteen bodies were found to contain 5 to 45 per cent. of fat emboli in the organs. The fat emboli were most numerous in the lungs. In addition to the presence of fat emboli, there were certain circulatory alterations, as edema and hemorrhages, besides fatty changes of some of the organs. Edema of the brain was observed in seven, fat droplets in the blood stream noted at the time of necropsy in six, petechial hemorrhages, also noted at the time of necropsy, in the skin or organs in nine. In the lungs of all the bodies there were large numbers of fat emboli, and in half there were microscopic hemorrhages. In the heart muscle of thirteen bodies there were fat emboli, microscopic hemorrhages in twelve and fatty degeneration in six. In the kidneys of all fourteen bodies there were fat emboli, fatty degeneration in thirteen and microscopic hemorrhages in ten. In but six of the livers were emboli found, while in twelve there was venous engorgement and fatty infiltration, the latter being marked in seven. Fat emboli were also found in the brain, suprarenal, gastric mucosa, testis and spleen, in several instances.

Comparing the clinical symptoms of the fourteen patients, one does not find such diversity; on the contrary, the clinical pictures of all have many points in common. All the patients after a variable period of consciousness passed into a restless stage; and in twelve this took the form of delirium, eleven becoming so violent that restraint was applied, and a similar number passing from their delirium into a comatose condition. In all fourteen there was marked dyspnea, and the respiratory rate increased, the maximum rates averaging fifty-three per minute for the fourteen. This average was made from the rates recorded on the history sheets a few hours previous to death. Two of the patients developed Cheyne-Stokes respiration, four suffered from air hunger, and two developed a marked cough. The pulse in all became weak and shallow, the maximum averaging 153 for the fourteen. Urine and feces were passed involuntarily in twelve, and in the other two the records are incomplete. Thirteen of the patients came into the hospital with a normal or slightly subnormal temperature, and in all it rose steadily to the time of death, the maximum temperatures averaging 105.2 for the fourteen. The bones fractured were the femur in four patients, the humerus in three, the tibia and fibula in five, the calcaneous in one and the pelvis in one. The ages of the patients varied from 35 to 90, averaging 53. The time that they lived after injury varied from two to seventeen days, averaging six days. A more complete discussion of this study is given in the previous report, already referred to.

The failure to correlate the amounts of demonstrable fat emboli in the organs with the clinical symptoms was rather to have been

expected, for the amount of fat in the organs varies from time to time. Following a fracture in which fat is liberated from the bone marrow, absorption takes place through the regional veins and lymphatics which are torn by traumatism. The emboli are carried to the venae cavae, thence to the right heart, which pumps them to the lungs, where they become lodged in the capillaries. After a variable period some of the emboli are forced through the capillaries, are returned to the left heart, and are then sent into the general circulation to reach the various tissues, where they again become lodged in the capillaries. Here also they are forced through after a variable period, but are replaced by new emboli which had been temporarily arrested in the pulmonary circulation. The fat is finally excreted, at least in part, by the kidneys.

Observers along other lines of study have frequently noted a failure of correlation between morphologic lesions and functional disturbances. Barker,[2] who has carefully reviewed the literature on the relations of alteration of the central nervous system following various forms of injury, concludes that the correspondence lies in the finer structural alterations not discoverable by present methods of examination, admitting, however, that histologic alterations have functional equivalents.

In view of the marked cerebral symptoms so often occurring in fat embolism associated with fractures, notably delirium followed by coma, which is so frequently ascribed to alcoholism, a detailed study of the central nervous system was undertaken, with the hope of finding alterations which would establish a pathologic basis for these cerebral symptoms occurring after fractures. This study was suggested by Dr. LeCount, who kindly supplied me the brain of Case A.

LITERATURE

The history of the occurrence of fat emboli in the central nervous system and the resulting symptoms forms the largest and most interesting chapter of the subject of fat embolism. Scriba[3] cites Cohn as the first to describe fat emboli in the brain. Cohn in 1860 found them in the capillaries of the cortex, but thought that they were the result of degeneration of the arterial walls. Muller[4] also in 1860 described fat emboli in the choroid coat of the eye, and he is generally cited by writers as the first to describe fat emboli in human tissue. Bergmann[5] in 1873 called attention to cerebral fat embolism and suggested its clinical importance. Czerny[6] in 1875 named it as a possible cause of

2. Barker: The Nervous System, New York, D. Appleton & Co., 1901, Chap. 25.
3. Scriba: Deutsch. Ztschr. f. Chir., 1880, xii, 118.
4. Muller: Wurzb. med. Ztschr., 1860, i, 45.

death. Fenger and Salisbury[7] in 1879 were probably the first in this country to describe fat emboli, as well as multiple ecchymoses in the brain. At this time there were numerous case reports in which cerebral fat emboli or symptoms were mentioned, without contributing new facts. Scriba[8] in 1880 gives a good description of the brain changes. He found hyperemia, multiple small punctate hemorrhages, anemic areas, fat emboli in the capillaries; and in some of the animals in which he produced experimental oil embolism the brain was edematous and the ventricles dilated. He regarded the changes in the brain and cord as the most important lesions of fat embolism, declaring that death could occur only from changes in the nervous system. Later writers do not agree with this dictum. His account of the clinical symptoms is also complete. He mentions collapse, stupor, disturbances in the pupillary reaction, loss of consciousness, convulsions, coma, etc., and attributes them to changes in the brain. Payr,[8] 1899, recognized cerebral fat embolism as a distinct clinical form, and divided them into cerebral and pulmonary types. Hamig[9] in 1900 made a careful study of the clinical aspects of cerebral fat embolism. He reports five cases in which the patients developed the typical symptoms, and in all of whose brains fat emboli were found in the capillaries. He expressed the belief that the clinical symptoms are due to the secondary changes, as hemorrhage and degeneration, rather than the presence of the fat emboli in the vessels. He contends that following many fractures no distressing symptoms of fat embolism occur, although fat may be found in the urine as evidence of the occurrence of fat embolism; and since the brain receives a more direct and larger amount of blood than the kidneys, it must also receive a considerable amount of circulating fat.

As to the time of the appearance of the secondary changes, especially the hemorrhages, there are different opinions. Ribbert[10] says that they appear after the third day following the injury. Grondahl[11] found them after fifty hours; Warthin[12] after twelve hours. Ribbert thinks that one third of the deaths associated with fat embolism is due to changes in the brain; Grondahl puts the figure at one half. The latter divides the cerebral symptoms into three stages: the initial stage, before the onset of the symptoms; the second or restless stage, in which the patient frequently develops delirium, and the last or coma-

5. Bergmann: Berl. klin. Wchnschr., 1873, xxxiii, 385.
6. Czerny: Berl. klin. Wchnschr., 1875, xliv, 593.
7. Fenger and Salisbury: Chicago Med. Jour. and Exam., 1879, xxxix, 587.
8. Payr: Ztschr. f. orthop. Chir., 1899, vii, 338.
9. Hamig: Beitr. z. klin. Chir., 1900, xxvii, 333.
10. Ribbert: Cor.-Bl. f. schweiz. Aerzte, 1894, xxiv, 457.
11. Grondahl: Deutsch. Ztschr. f. Chir., 1911, cxi, 56.
12. Warthin: Internat. Clin., 1913, iv, Series 23.

tose stage. Amberg[13] lays great stress on the recognition of the initial stage as an early diagnostic point of fat embolism. As pointed out by Benestadt,[14] the changes in the brain are not necessarily fatal. He reports the cases of three patients who developed symptoms of fat embolism following fractures of bones. All three passed through the first two stages and subsequently recovered. Godlee and Williams[15] contribute a valuable article on cerebral fat embolism in which the association of the cerebral symptoms and brain changes seem to be quite evident. In a railroad accident there were nineteen persons who sustained fracture of one or more bones. Of these, four died, one almost immediately, and the other three after different periods following the accident. In one of the last three a postmortem was not allowed, but in view of the almost identical symptoms, they think that he also possessed the same anatomic changes. One patient suffered from a simple fracture of the femur. He was brought to the hospital within one hour and had not lost consciousness, but that evening he became comatose and could not be roused. His pulse was 130, temperature 103, and respiration was of the Cheyne-Stokes type. He remained in coma and died four days later. Another patient suffered from a crushing injury of both femurs. He also was fully conscious when brought to the hospital, but within a few hours he became restless, his pulse was 160, temperature 102, and rapid respiration of the Cheyne-Stokes type. The following morning he became comatose and died on the second day. The brains of these two patients contained many punctate hemorrhages, and on microscopic examination the capillaries were found filled with fat emboli, and there were numerous small hemorrhages.

In our series all the patients developed marked cerebral symptoms. Five were brought to the hospital in the restless stage, and one was wildly delirious. In the case of these five a period of several hours had elapsed after the injury. The others suffered from no distressing symptoms on admission, but became restless in twelve to twenty-four hours. Most of them lay for hours at a time muttering incoherently, tossing about their beds and trying to get up. They became stuporous in twelve to thirty-six hours, and gradually comatose in twenty-four to seventy-two hours, from which they could be aroused at first by supraorbital pressure, but later failed to respond. One patient partly recovered from his symptoms, but had a relapse, and two remained delirious for about ten days. In two patients the pupils were constricted on admittance, but dilated before death; one developed ptosis of one lid subsequent to his admittance and one strabismus.

13. Amberg: Wien. klin. Rundschau, 1914, xxviii, 95.
14. Benestadt: Deutsch. Ztschr. f. Chir., 1911, cxii, 194.
15. Godlee and Williams: Lancet, London, 1911, i, 1062.

EXPERIMENTAL DEMONSTRATION OF THE INFLUENCE OF FAT ON THE CIRCULATION

In order to obtain some idea of the processes that take place in the capillaries following the entrance of fat emboli, the following experiments were devised to study the viscosity of the blood in fat embolism, also the capillary resistance associated with the altered conditions of the blood. It is realized that these capillary experiments cannot be held a strict counterpart of the phenomena that take place in the blood vessels, in view of the ability of the blood capillaries to alter their physiologic state in response to altered physical states of the blood; nevertheless, for a given instant, the conditions may be regarded as being analogous. The experiments were repeated a sufficient number of times to insure uniformity of results.

To determine the alterations in the viscosity of the blood, a simple apparatus was set up for measuring the rate of flow of fluids through a long capillary tube of a small bore, under constant pressure. The apparatus consists of a capillary tube 30 cm. long having a bore of less than 1 mm. connected with a 5 c.c. glass bulb used as a reservoir for the fluids to be tested, which in turn is connected with a buret containing a column of water having a pressure of 70 mm. mercury. A T tube placed between the bulb and the buret is used to empty and refill the bulb (Fig. 15). One cc. of the fluid was allowed to flow through the capillary, the amount being determined on the buret. A series of fluids was then examined, for the rate of time that it required 1 c.c. to flow through the capillary; in each instance the experiment was started with the column of water in the buret having a pressure equal to 70 mm. mercury. Emulsions were then made, using 9 c.c. of each of the respective fluids and 1 c.c. olive oil, and the rate of flow determined. To insure the proper escape of the emulsions through the capillary, the bulb was placed slightly lower than the capillary; and to eliminate the source of error due to alterations of the emulsions by mixture in the T tube, only the first cubic centimeter was measured, the remainder being discarded. The following results were obtained:

TABLE 1.—TIME REQUIRED FOR ONE CUBIC CENTIMETER OF FLUID TO PASS THROUGH THE CAPILLARY UNDER CONSTANT PRESSURE OF 70 MM. HG. AND CONSTANT TEMPERATURE OF 24.5 C.

	Alone. Seconds	Plus Olive Oil. Seconds
Salt solution	33	100
Ascitic fluid	45	130
Human blood serum	57	180
Human blood slightly diluted with citrate solution	160	480

As seen from the table, the viscosity of the blood is increased approximately four times in these experiments, which gives ground for the belief that a similar increase may occur in fat embolism. In study-

ing the resistance occurring in capillary tubes the same apparatus was used, the resistance being measured in terms of millimeters of water as determined by the height of the column in the buret required to force the fluid through the capillary. The system was filled with water until the water level in the buret was the same as in the capillary. In this condition no fluid escaped from the open end of the capillary. The column of water was then raised until the fluid just escaped from the capillary. The column of water above the capillary being read in millimeters was taken as the pressure necessary to overcome the capillary resistence. The same series of fluids was tested. The figures in the first column of the following table give the pressure required to cause the several fluids to pass through a capillary 205 mm. long and one-fourth mm. in diameter. In the second column is given the pressure required after the addition of olive oil, mixed as in the previous experiment. It is seen that it required approximately ten times the pressure after the addition of the oil. Various sized capillaries ranging from 10 microns to 1 mm. in diameter were used, and the same principle was observed in all. The figures, however, denote only approximate relationships, for one of the variable factors was the size of the oil droplets, and this factor we were able to control only approximately. The principle, however, of increased capillary resistance of fluids following the addition of oil nevertheless holds true.

TABLE 2.—Pressure in Millimeters of Water Required to Overcome the Capillary Resistance of a Tube 205 mm. Long and One-Fourth mm. in Diameter; Temperature 23 C.

	Alone, mm.	Plus Olive Oil, mm.
Salt solution	4	41
Ascitic fluid	5	46
Human blood serum	5	49
Human blood slightly diluted with citrate solution	11	95

These tables at least give an idea of the processes taking place in the capillaries, and help explain the obstruction to the circulation which results in the observed phenomena of focal edema, focal hemorrhages and focal necrosis following the entrance of fat into the blood vessels.

REPORT OF CASE *

The clinical history and pathologic alterations of the subject of this study are as follows: Patient A, a railroad fireman, 35 years old, was struck on the head by a projection of a low viaduct while removing the signal flags from the top of the tender, Oct. 4, 1909. He was picked up unconscious by the engineer, who said that the patient's leg was doubled under him. He was

* As noted in the previous report (LeCount and Gauss, loc. cit.) Dr. Evarts A. Graham reported some of the details of this case of fat embolism to the Illinois State Medical Society March 23, 1910, but so far as known did not have them published.

brought to the Presbyterian Hospital, several hours later, and by this time had recovered consciousness. There was found on examination a superficial scalp wound over the left anterior parietal region, although no skull fracture could be determined, a fracture of the tibia at the junction of the middle and lower thirds, and a fracture of the fibula above that of the tibia. A diagnosis of the fracture of the tibia and that of the fibula of the left leg was made, to which was added later, complication by fat embolism.

The patient lived four days. On admittance he was fully conscious and answered all questions, though somewhat slowly. His pupils were equal and exhibited no abnormal signs. The muscular power was equal in both hands, there was good movement of the toes, the general cutaneous sensations were equal on both sides, the tongue was extended in the median line when the patient was asked to do so, and he did not complain of headache or dizziness. He remained quiet all day, but toward evening complained of pain. He took nourishment when fed, and appeared dull mentally. He slept nearly all of the night. On October 5 he awoke at 8 a. m., and complained of pain in the back. He became restless and morphin was administered, but the restlessness continued during the morning and afternoon. In the late afternoon he became drowsy, then stuporous and failed to respond to questions. He was temporarily aroused by supra-orbital pressure. He ate little. On October 6 he was in coma; the pupils had contracted to pinpoint size, the eyes were turned upward, and there was a slight strabismus with deviation to the left. Later in the day the pupils enlarged, and the patient sank deeper into coma, from which he could not be aroused to consciousness, by supra-orbital pressure. He continued in this state to the time of his death, October 7, at 3 p. m. The respiration on admittance was normal in rate and rhythm. On the morning of October 5 it became irregular; by the afternoon it developed into the Cheyne-Stokes type, in which form it continued. On October 7 the patient developed singultus, the breathing became labored, and there was dulness and bronchial breathing over the right lower lobe posteriorly and many coarse râles were heard. The respiratory rate, which had been steadily increasing, reached 64 per minute before his death.

The pulse was normal on admittance, with a rate of 74. It increased steadily, reaching 164 per minute before his death. On October 6 the patient became cyanotic, this condition becoming more marked the next day. Blood drawn from the patient contained fat droplets. The patient perspired profusely during the last few days. Urine and feces were passed involuntarily. Petechial hemorrhages were first noticed at 8 a. m. on October 5, in the scapular regions. They developed rapidly, breaking out in crops. On the morning of October 6 they were all over the trunk, and by noon the neck was also covered with them. The temperature on admittance was 97.8. It rose steadily during the four days, reaching 106.2 before his death.

The postmortem examination was performed the following morning by Dr. E. R. LeCount. Anatomic diagnosis: "Comminuted fracture of the tibia; fracture of the fibula and skull; petechial hemorrhages of the skin, conjunctiva, serous and mucous membranes; parenchymatous hemorrhages of the lungs; hemorrhages in the anterior mediastinum; infarction of both testicles, with fatty changes; icterus; cloudy swelling of the kidneys; recent operative wound of the head; therapeutic puncture wounds of the trunk (sodium chlorid infusion); latent tuberculosis of the lungs; fibrous pleuritis and peritonitis; fibrous mural endocarditis; edema of brain."

From the necropsy record the following items are taken: "Over the trunk, especially the upper part, were innumerable minute petechial hemorrhages, which were in some places clustered, but over the upper part of the chest they were 1 cm. apart. In the pericardium were numerous petechial hemorrhages, which varied in size, some being 1 cm. long and irregular. The lining of the right heart chamber contained numerous small hemorrhages. Both of

the testicles were studded with minute hemorrhages. In the roof of the left orbit there was a fracture, obliquely directed, 2.5 cm. long, with the forward end out. There were small hemorrhages in the gastric mucosa."

In microscopic preparations fat emboli were found in the brain, lungs, myocardium, kidneys, suprarenals, liver and testis. All sections of the lung contained emboli in large amounts. They were well distributed in the capillaries throughout the lung. In shape the emboli were round, oval or elongated; in size from 10 to 50 microns. Under high power there were observed many capillaries running across the microscopic field filled and distended with strings of emboli. The arteries and capillaries were engorged. There were scattered areas of lung tissue in which the alveolar spaces were filled with a hemorrhagic exudate. All sections of the kidney contained emboli, found chiefly in the capillaries of the glomeruli. Nearly all the glomeruli contained some emboli, and about one third were completely blocked by them. In shape the emboli were irregular and tortuous, lying in and distending the glomerular capillaries. Many of the vasa afferentia contained elongated emboli at the entrance to the glomerulus, some 50 to 80 microns in length. The capillaries and arteries were engorged, and there were small intertubular extravasations of blood.

The liver contained emboli in small amounts, found in the capillaries between the hepatic cords. In some of the sections there were capillaries measuring about 100 by 30 microns, which were filled with strings of emboli from 20 to 30 microns in diameter. Near the central veins of many of the lobules the hepatic cells had undergone fatty degeneration. Many of the capillaries just beneath the hepatic capsule contained emboli. There was venous and capillary congestion. All sections of the heart contained emboli, chiefly in the capillaries between the muscle cells. They were round, oval, elongated or spindle-shaped and from 10 to 40 microns in diameter. The muscle cells adjacent and near the emboli had undergone fatty degeneration. These areas of fatty degenerated tissue, containing emboli, were separated from each other by normal tissue in which there were few or no emboli. There was also considerable infiltration of the myocardium by fatty areolar tissue. The arteries and capillaries were distended with blood.

Most sections of the suprarenal contained emboli in the capillary sinuses between the cells of the zona fasciculata, also in the zona glomerulosa. The emboli were elongated and from 20 to 40 microns. In the zona fasciculata there were distended straight capillaries running across the high power microscopic field filled with emboli of various sizes and shapes. The parenchyma cells contained more than the usual amount of fat, especially in the zona fasciculata. A few sections of the testis contained emboli in the capillaries about the seminiferous tubules, from 10 to 20 microns, and usually elongated. The interstitial tissue contained numerous fine fat droplets, suggesting fatty degeneration. The seminiferous tubules were normal.

Study of Brain.—The brain was placed in 10 per cent. dilution of liquor formaldehydi for preservation, and in this condition it was received for study. The brain was normal in size, weight and configuration. The gyri were of normal width and the sulci of normal depth. The pial vessels were moderately engorged. The arteries at the base of the brain were collapsed and there were small regions of thickening in the basilar, posterior cerebral, and middle cerebral arteries. On surfaces made by sectioning the brain transversely there were several small hemorrhages in the anterior half of the corpus callosum, especially in the genu. These hemorrhages measure from 0.5 to 2 mm. in diameter. They were well defined, sharply limited and generally were round or slightly irregular. Similar punctate hemorrhages were found in the white substance throughout the entire cerebrum, especially in the frontal and parietal lobes. The lateral ventricles were moderately dilated.

A preliminary examination of sections taken from the frontal, parietal and occipital lobes was made, and there were found in all the sections fat emboli,

hemorrhages, and foci of degeneration. A more detailed study of this brain was undertaken to (*a*) identify these alterations with relation to the intrinsic circulation of the encephalon, (*b*) to study the finer histologic alteration in the areas of focal degeneration by means of differential stains, and (*c*) to localize the lesions with reference to the various functional centers and pathways of the brain.

It became evident that an accurate identification of the various sulci and gyri of the brain was essential. This was done with the aid of numerous standard textbooks on the morphology of the brain, which were freely con-

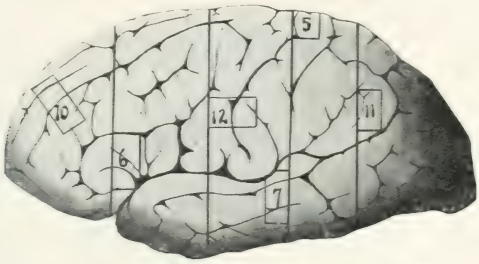

Fig. 1.—Plot of brain, giving lateral view of convex surface of the left cerebral hemisphere, and showing configuration and the location of the sections removed for study; reduced.

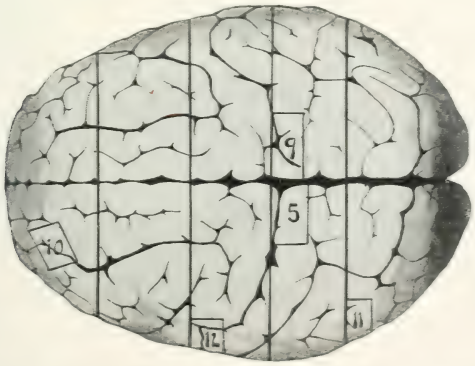

Fig. 2.—Plot of brain, representing convex surface from above, and showing configuration and the location of sections removed for study; reduced.

sulted. The brain was then accurately plotted. Four views were made; a lateral view of the left hemisphere (Fig. 1), a view of both hemispheres from above (Fig. 2), a view of a transverse section just anterior to the mammillary bodies (Fig. 3), and a mesial view of the left hemisphere (Fig. 4). These plots were made as follows: A plane resting on a prominent point of the cortex was imagined, all points of the sulci projected to it by parallel lines, measured with a ruler and drawn; that is, it is as if a piece of glass were laid on the brain, which being held firmly in the desired position, its configuration was copied with a wax pencil, the range of vision being kept constant.

It would of course have been desirable to examine all of the functional areas of the brain; however, such a study was beyond the scope of our present effort, and consequently only representative areas were examined, these being chosen from the more important known centers. They were taken from the following regions as indicated in Figures 1, 2, 3 and 4:

1. Spinal cord at the upper border of the decussation of the pyramidal tract.
2. Vermis cerebelli.
3. Right cerebellar cortex and dentate nucleus.
4. Left cerebellar cortex and dentate nucleus.
5. Left cerebral cortex, central sulcus, leg area, sensory and motor sides.

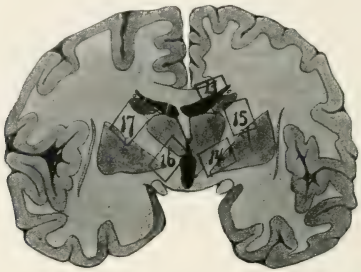

Fig. 3.—Plot of brain, representing transverse section just anterior to the mammillary bodies, and showing the location of the sections removed for study in relation to the internal capsule and the internal nuclei; reduced.

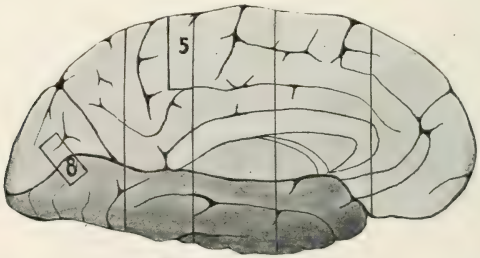

Fig. 4.—Plot of brain, representing mesial surface of left cerebral hemisphere, and showing configuration and location of sections removed for study; reduced.

6. Left cerebral cortex, triangular part of inferior frontal gyrus, motor speech area (Broca's convolution).
7. Left cerebral cortex, superior and middle temporal gyri, auditory area.
8. Left cerebral cortex, calcarine fissure, including portions of the cuneus and lingual gyri, vision area.
9. Right cerebral cortex, leg area, central sulcus, including sensory and motor sides.
10. Left cerebral cortex, superior and middle frontal gyri, association area.
11. Left cerebral cortex, gyrus angularis, inferior parietal lobule, association area.

12. Left cerebral cortex, central sulcus, arm area, including sensory and motor sides.

13. Body of corpus callosum near the middle of its anteroposterior extent, right side.

14. Right ventral limb, internal capsule, including portions of the globus pallidus and thalamus. This and the following three sections were taken from a transverse section of the brain just anterior to the mammillary bodies.

15. Right dorsal limb, internal capsule, including portions of the putamen and caudate nucleus.

16. Left ventral limb, internal capsule, including portions of the globus pallidus and thalamus.

17. Left dorsal limb, internal capsule, including portions of the putamen and caudate nucleus.

Large blocks of tissue several centimeters in length were removed from these areas, and these in turn were cut into smaller blocks and rehardened, frozen and cut, or embedded in paraffin or gelatin, according to the need. In order to bring out as many of the neurologic elements as possible, as well as the pathologic lesions, a variety of stains were used, including sudan III, osmic acid, hematoxylin and eosin, Mann's methylene-blue eosin, toluidin-blue Nissl stain, phosphotungstic acid hematoxylin, Marchi, Golgi, Weigert's myelin sheath stain, Weigert's neuroglia stain, the Ranson-Cajal neurofibril stain, Bielschowsky neurofibril stain, Heidenhain iron hematoxylin stain, Apathy after-gilding chlorid stain. These stains were adapted to the material examined. In view of certain postmortem alterations which occurred in the central nervous system, sections of another brain obtained about the same time and preserved in a similar manner were run in a parallel series as a control, to eliminate artifacts of preparation and postmortem changes.

The alterations will be discussed under the several headings of edema, hemorrhages, fat emboli, focal necrosis, changes in the nerve cells, round cell infiltration, changes in the spinal tracts.

Edema: This condition was observed in the fresh brain at the time of the postmortem. At the present examination after formaldehyd fixation, the ventricles are moderately dilated. It is of course impossible to make any observation of the intermeningeal fluid content. Microscopically, many of the ganglionic cells of the dentate nucleus and of the pyramidal layer of the cerebral cortex are slightly swollen; in the Purkinje layer of the cerebellum there also occur groups of cells that appear swollen. In the cerebral cortex there are present small diffuse areas that suggest focal edema. These areas are associated with fat emboli, and are found principally in the portion included by the lamina granularis interna and the lamina multiformis, and in the molecular layer of the cerebellum. These focal areas are irregular in shape and cover an area whose greatest diameter varies from 500 to 900 microns. Observed in sections stained with Mann's methyl-blue eosin,[16] there are seen scattered through these areas empty capillaries, markedly distended, round or oval in outline, which represent the site of fat emboli. About these vessels are irregular shaped small clear spaces that are extravascular. The extravascular spaces are much more numerous than the larger, definite intravascular spaces, and they comprise the bulk of the focus. The neurophil in these foci appears slightly compressed.

Hemorrhage: Grossly punctate hemorrhages are easily seen in the anterior genu of the corpus callosum and in the white substance beneath the cortex of the cerebrum (Figs. 5 and 6). Microscopically, small hemorrhages are found in all the blocks removed for study. Of each block of tissue removed for study, from

16. Encyklopädie der Mikroskopischen Technik, Berlin, 1903, i, 262.

fifty to two hundred sections were examined, and in about half of these hemorrhages are present. The distribution is uniform in all the blocks when compared to each other. In the spinal cord they occur principally in the gray matter. In one run of sections, the posterior horn, the gelatinous substance of Rolando is a common site (Fig. 7). In the cerebellum a count of one hundred hemorrhages was made. There are forty-four in the granular layer, thirty-two about the Purkinje cells, twenty-one in the molecular layer, two in the dentate nucleus, and one in the medullary substance. In a count of one hundred in the cerebral cortex, the three blocks removed from the central sulcus being used, the distribution is as follows: one in the lamina zonalis, four in the lamina granularis externa, fourteen in the lamina pyramidalis, three in the lamina granularis interna, seventeen in the lamina ganglionaris, twenty-four in the lamina multiformis and thirty-seven in the medullary substance. In the corpus callosum, internal capsule and portions of the adjacent caudate, thalamus and lentiform nuclei, the hemorrhages are present in large numbers (Fig. 8). The hemorrhages cover an area whose largest diameter varies from 100 to 700 microns, generally 300 to 500. They are sharply defined, round or oval in outline, commonly placed about a capillary, the lumen of which is distended, appears empty in the paraffin sections, but is frequently seen to contain a single fat embolus in the gelatin-embedded and fat-stained sections. The hemorrhages are compact, but occasionally appear as circular bands (Fig. 9).

Fat Emboli: These are present in every section stained with sudan III or osmic acid, after gelatin embedding or frozen section. In the spinal cord they are present in both the white and gray substance, more frequently in the latter. In the cerebellum the order of frequency is as follows: molecular layer, Purkinje layer, dentate nucleus, granular layer, and medullary substance. In the cerebrum they are present in largest numbers in the middle layers of the cortex included in and between the lamina pyramidalis and lamina ganglionaris. The peripheral layers and medulla contain lesser amounts. The number of fat emboli per low power microscopic field varies from ten to fifty, they are long, cylindrical, club shaped, or occur in strings of small, round globules, and some of the longer emboli measure 100 microns in length. Many occlude the vessel in which they lie, and branch with it at a point of bifurcation (Fig. 10). In some of the microscopic fields measuring 250 microns under high power, there are capillaries running across the field that are filled with emboli.

Focal Necrosis: In addition to the areas described under "focal edema," characterized by a diffuse area containing many small clear spaces surrounding the sites of multiple fat emboli, there are present smaller, sharply defined areas which will be described under the term "focal necrosis." The appearance of these areas varies somewhat with the stain employed. They are, however, observed with most of the stains used. Within their border there seems to be a loss of some of the neurologic elements, so that they appear as light staining areas surrounded by the normal darker staining tissue. These areas are round, oval or spindle shaped, and frequently placed about a single capillary occluded by fat emboli. In the methyl blue eosin preparations there appears to be a loss of the eosin staining elements. The loss is most marked toward the periphery of the focus where it terminates abruptly at the border; towards the center of the lesion the loss is less marked. In some of these there is an increase of the neuroglia cells in the centers. In other foci the loss of tissue is uniform, the center and periphery staining alike. A few foci with clear centers are surrounded by hemorrhagic bands, suggesting the hemorrhagic infarct. In the phosphotungstic acid hematoxylin preparation there is a loss of the blue staining elements, with an apparent decrease of the neuropil or *Punktsubstanz*, the fine granular background of the tissue. In Weigert myelin sheath stained preparations definite information is obtained of these foci. Here is seen a loss of the

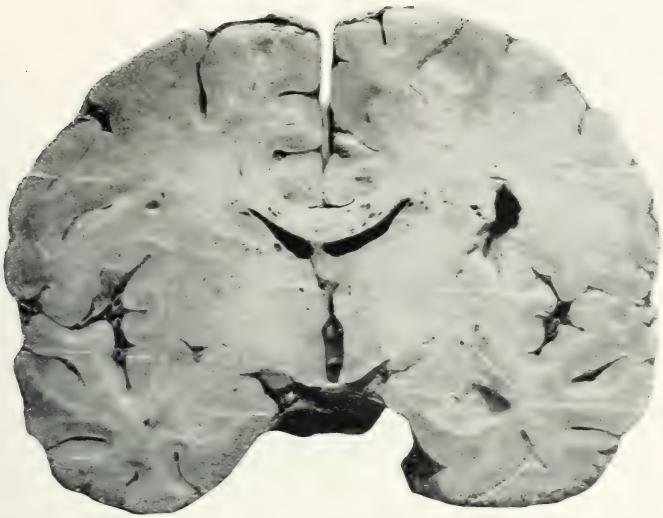

Fig. 5.—Photograph of transverse section of brain just anterior to the mammillary bodies. In the corpus callosum there are punctate hemorrhages.

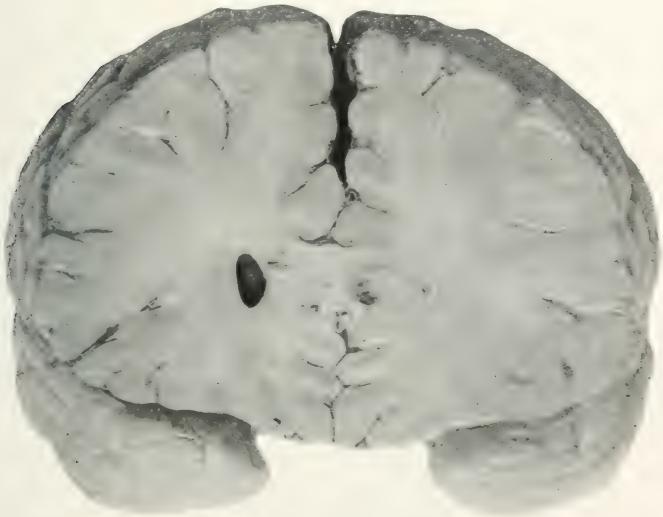

Fig. 6.—Photograph of transverse section of brain just anterior to the poles of the temporal lobes. In the corpus callosum and frontal lobes there are punctate hemorrhages.

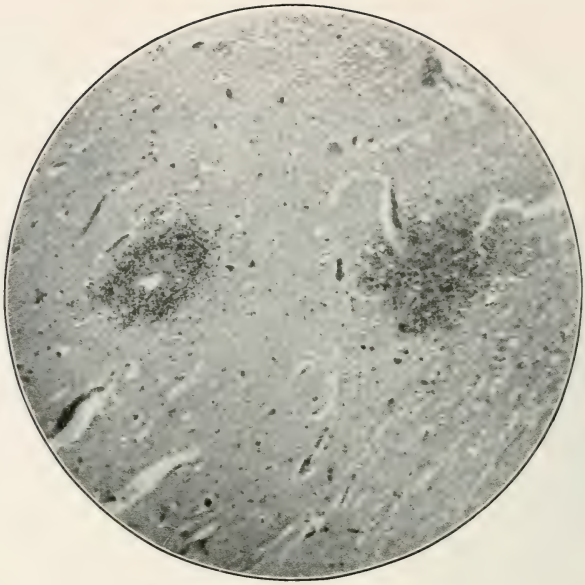

Fig. 7.—Photomicrograph, × 110, showing hemorrhage and round cell infiltration into the gelatinous substance of Rolando, dorsal gray horn of spinal cord at level of decussatio pyramidum; methyl blue eosin stain.

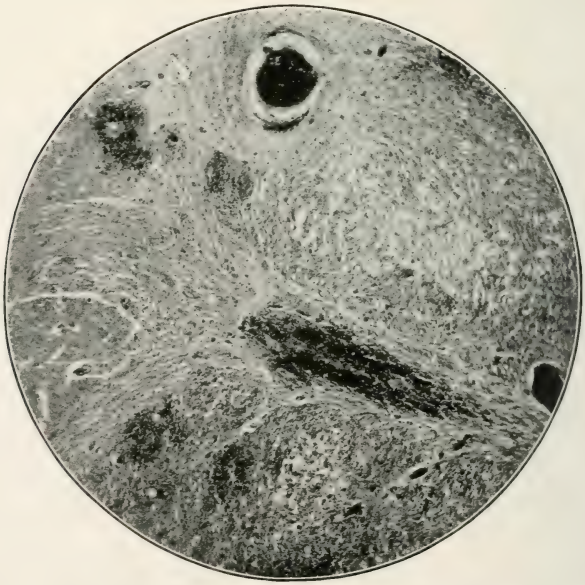

Fig. 8.—Photomicrograph, × 60, showing hemorrhage and round cell infiltration into the ventral limb of the left internal capsule; at left of the photomicrograph is an adjacent portion of the thalamic nucleus, taken from a transverse section of the brain just anterior to the mammillary bodies; methyl blue eosin stain. Block 16.

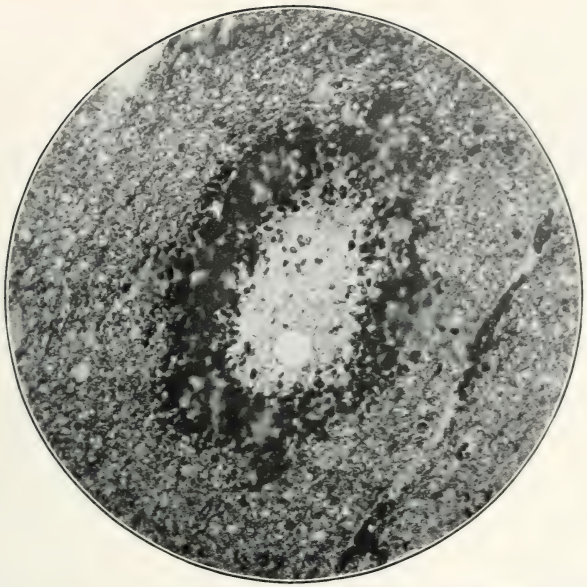

Fig. 9.—Photomicrograph, × 230, showing circular hemorrhage in the leg area of the precentral gyrus, right hemisphere; Weigert myelin sheath stain. Within the hemorrhage the myelin sheaths are entirely destroyed.

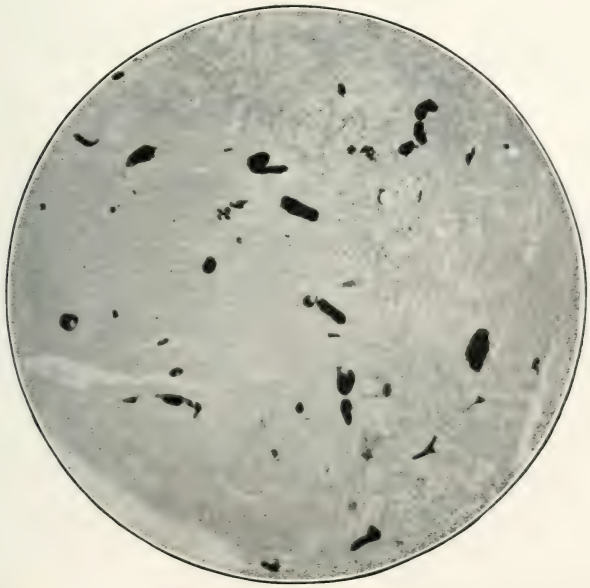

Fig. 10.—Photomicrograph, × 110, showing fat emboli in cerebellar cortex; osmic acid stain.

myelin sheath (Fig. 11). In some of the foci, there is a total loss of the myelin sheath, but in general a few sheaths are present, these being thinner and more granular than the sheaths of the surrounding tissue, although occasional strands of sheaths traverse the focus and appear to be unaltered. In a few foci seen in the leg area of the left central sulcus a peculiar type of lesion is present. It is a circular hemorrhage, within which there is a total loss of myelinated fibers (Fig. 9). In the silver-pyridin preparation for neurofibrils further information is obtained of these foci. Here is seen a loss of neurofibrils. In the lesions found in the medullary substance of both cerebrum and cerebellum this means a localized destruction of the axones. In some of these foci nearly all of the neurofibrils are lost, in others varying amounts up to about one fourth remain[17] (Fig. 12).

Within the focus the remaining neurofibrils are more irregular and broken up than in the surrounding tissue, although here also a few unaltered strands are present. These foci are present in every block of tissue removed for study and in the majority of the sections. As many as six to the low power field are observed. All parts of the brain are equally affected, there being no noticeable difference in the sections from the various areas of the cerebrum or cerebellum. Within each section they seem to predominate in the regions of the myelinated axons. In one hundred counted in the cerebellum there are forty-three foci in the dentate nucleus, thirty-eight in the medullary substance, fourteen in the granular layer, and five about the Purkinje cells. In the cerebrum, one hundred foci being counted, all are in the medullary substance or in the cortex immediately adjacent to it.

Nerve Cell Changes: The loss of myelin sheaths and axons demonstrable in the preparations just discussed permits an interpretation of the changes in the nerve cells with a greater degree of certainty. The dentate nucleus is a very common site of the focal necrosis. Many of the ganglionic cells in the region of these foci, including those cells within the focus, immediately adjacent to it or a short distance from it, appear to have undergone profound changes. The Weigert preparation, in which destaining had been arrested before the cell bodies were fully decolorized, was chosen for this study because in it are seen the cell changes in relation to the focal necrosis of the myelin sheaths. A normal cell in this preparation is polygonal in shape and has a definite outline, although no definite cell membrane is visible; there are several dendritic processes attached to it for a short distance. The cytoplasm is finely granular and stains deeply, the nucleus is centrally placed, generally round in shape, occupies about two fifths of the diameter of the cell, contains a dark intensely staining nucleolus centrally or slightly eccentrically placed, which is surrounded by a clear zone containing some light staining chromatin. In the early changes observed in these cells there is a shifting of the nucleus so that it occupies an extremely eccentric position, coincident with the cell assuming a round or oval appearance in place of the more polygonal form; the cytoplasm may still stain deeply. In other cells the nucleus has remained central, but the nucleolus occupies an extremely eccen-

17. Our material had been in formaldehyd for several years. Several neurofibril stains were tried with unsatisfactory results. A definite, clear-cut picture of the axons and dendrites that would permit of quantitative as well as of qualitative study was not obtained, either through faulty technic or acid reduction of the neurofibrils by the commercial formaldehyd used as the preservative. After numerous trials, it was found that if small pieces of tissue 1 cm. square and not over 2 mm. thick were placed in a 1 per cent. ammonia solution for twenty-four hours with repeated changes, then placed in a 1 per cent. ammoniacal 95 per cent. alcohol for seventy-two hours, with repeated changes, then fixed according to the method given by Ranson (Jour. Comp. Neur., 1912, xxii, 487) starting with 1 per cent. ammoniacal absolute alcohol and increasing the period of silver impregnation to from four to five days, a very satisfactory neurofibril preparation resulted from the formaldehyd fixed material.

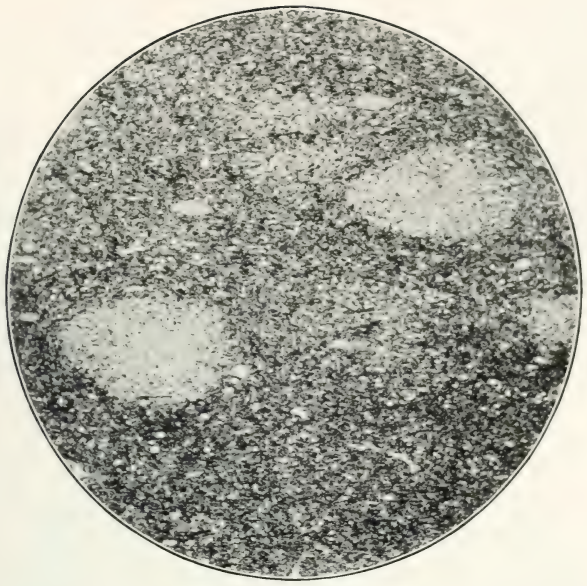

Fig. 11.—Photomicrograph, × 60, showing multiple foci of necrosis in the arm area of the precentral gyrus, left hemisphere; Weigert myelin sheath stain. In the light staining areas there is a loss of most of the myelin sheaths.

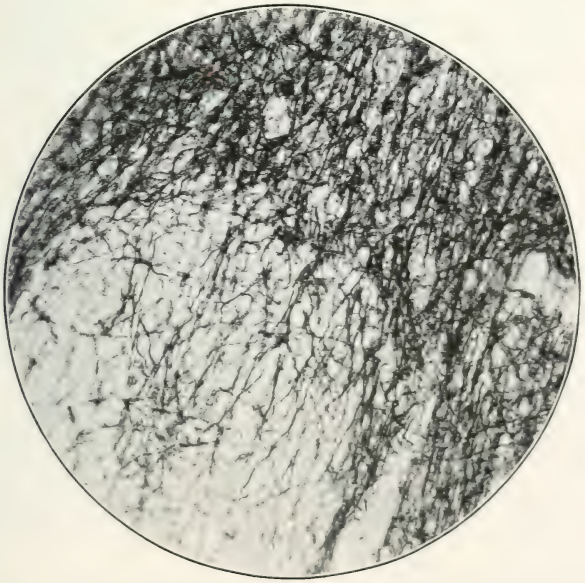

Fig. 12.—Photomicrograph, × 325, showing focal necrosis in the motor speech area from the triangular part of the inferior frontal gyrus of the left hemisphere. Silver pyridin preparation for neurofibrils. Within the focus four fifths of the axons have been destroyed.

tric position. The cells that have undergone further changes look swollen with the entire pattern slightly blurred. The cytoplasm stains lightly, the nuclear membrane is irregular, broader and less distinct; the nucleus appears swollen and may occupy one third to one half of the diameter of the cell; the nucleolus is also swollen and less distinct; and there is an increase in the stainable nuclear chromatin. In still later changes the nucleus has entirely disappeared and all that remains of the cell is a round or club shaped mass of granular, irregular staining protoplasm, containing a lighter staining round area placed near its center or eccentrically (Fig. 13). These changes are observed in many of the cells of the dentate nucleus and to a lesser extent in the pyramidal cells of the cerebrum. Whether they are consequent on the changes in the axons and myelin sheaths cannot be determined on the basis of this single study; although

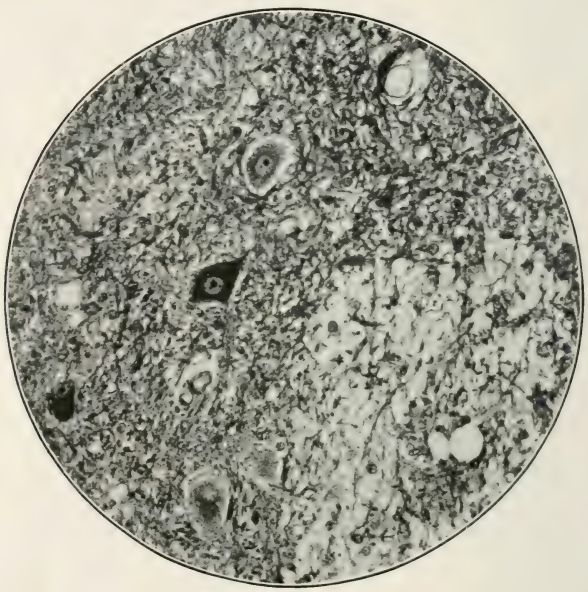

Fig. 13.—Photomicrograph, × 275, showing changes in the dentate nucleus; Weigert stain. In the lower right quadrant there is an area of focal necrosis in which most of the myelin sheaths are lost. Two ganglionic cells immediately adjacent to it have undergone karyolysis and partial cytolysis. A cell in the left lower quadrant has an eccentric nucleus; the dark staining cell in the center of the field is normal, and the cell above it stains lightly.

in all probability some relation exists between them. Warrington[18] has carefully studied the structural alterations of nerve cells following injury to their processes. On cutting the posterior spinal nerve roots in cats and monkeys he observed profound changes in the ganglionic cells of the posterior root; and on cutting the anterior spinal roots he observed marked changes in the corresponding cells of the anterior horn of the spinal cord. *The results enabled him to accept*

18. Warrington: Jour. Physiol., 1898, xxiii, 112.

as a general law that in a cell loss of continuity of its processes is followed by definite structural changes. He reviews the work of Marinesco, Lomy, Ballet, Munzer and Wiener to show that nerve cells undergo profound changes in consequence of disturbances of the vascular system; and he cites Nissl to the effect that nerve cell alterations may appear within twenty-four hours after injury to the processes.

Round Cell Infiltration: This lesion occurs less uniformly than any of the previously described lesions, and is generally associated with hemorrhages occuring near or adjacent. The infiltrated area differs from the hemorrhages in that while the hemorrhages are found sharply limited and round, the infiltrated areas tend to be diffuse and bear no special relation to the blood vessels.

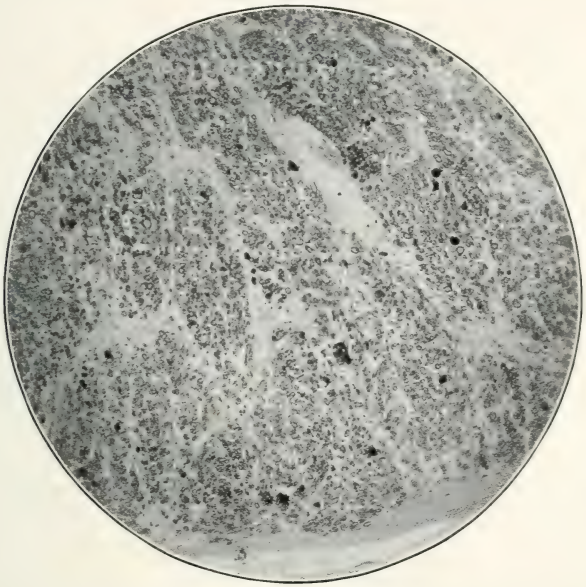

Fig. 14.—Photomicrograph, × 110, showing degenerated nerve fiber sheaths, Marchi preparation, in the fasciculus anterolateralis of the spinal cord at the level of the decussatio pyramidum.

Changes in the Spinal Tracts: To determine what, if any, were the effects of the various lesions of the cerebellum and cerebrum on the pathways of the spinal cord, a block of cord was prepared by a slight modification of the Marchi method for degenerated myelinated fibers. This section was taken at the level of the decussatio pyramidum, and contains in the dorsal funiculus the fasciculus gracilis and the fasciculus cuneatus and their nuclei, of which a few fibers from the nucleus of the fasciculus cuneatus pass anteriorly to form the lower border of the medial lemniscus. In the funiculus lateralis there are the fasciculus lateralis proprius, the fasciculus cerebellospinalis of the Basle anatomical nomenclature, properly called the tractus spinocerebellaris dorsalis by Herrick[19] and others, and the fasciculus anterolateralis, which includes the tractus

19. Herrick: An Introduction to Neurology, 1915, Chap. 8.

spinocerebellaris ventralis, the spinal lemniscus of Herrick or the tractus spinothalamicus of Cunningham,[20] the tractus rubrospinalis. In the funiculus ventralis there is the narrow bundle of the fasciculus proprius ventralis on either side and the rather large pyramids of the fasciculus cerebrospinalis, which cross the midline and deflect the anterior sulcus. The spinal V tract is lateral to the substantia gelatinosa Rolandi, and there are portions of the dorsal and ventral spinal roots attached.

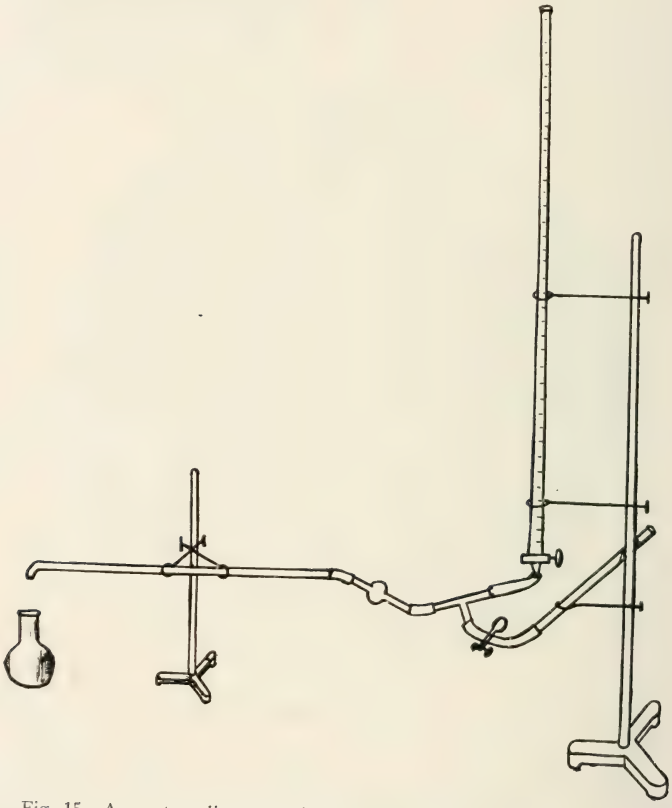

Fig. 15.—Apparatus, diagrammatic, used in studying viscosity and capillary resistance.

In the funiculus ventralis, there are numerous degenerated fibers scattered among the normal fibers. The degenerated fibers form about 1 to 2 per cent. of the total number. They are uniformly distributed throughout the funiculus. In the funiculus lateralis, both in the ascending and the descending tracts, and in the spinal V tract there are degenerated fibers (Fig. 14); the number in

20. Cunningham: Text Book of Anatomy, New York, 1909, p. 468.

this funiculus is not so large as in the funiculus ventralis and the largest numbers occur in the fasciculus spinocerebellaris. In the funiculus dorsalis the degenerated fibers are present in about the same proportion as in the funiculus ventralis, and in the adjacent portions of the spinal roots a moderate number of degenerated fibers are present. The presence of degenerated fibers in the descending pathways was expected after demonstration of frequent nerve destruction at the higher levels, and their presence in the ascending pathways was anticipated. In view of the wide and uniform distribution of the lesions in those parts of the central nervous system examined it seemed not unlikely that they should also occur in other parts. The demonstration of degenerated fibers in the spinal roots and ascending pathways is strongly suggestive of lesions in the lower part of the cord and the more peripheral nerves, that were not available for study.

CORRELATION OF CLINICAL AND ANATOMICAL FINDINGS

In attempting to correlate these lesions with the clinical symptoms, it first becomes necessary to establish the alterations in the physiologic pathways of the central nervous system. In view of the various descriptions given to these tracts by authors, we shall for uniformity follow the nomenclature and descriptions given in chapters 8 and 9 of Herrick's Introduction to Neurology. It is not essential to correlate every observed lesion with these tracts. It is sufficient simply to establish an alteration of each of the constituent neurons, namely, the peripheral sensory neuron of the first order, the central neuron of the second order, etc.

In the exteroceptive conduction paths there are at the level of the neurons of the first order degenerated fibers in the dorsal spinal root; of neurons of the second order degenerated fibers in the spinal lemniscus; of neurons of the third order hemorrhage and destruction of nerve fibers in the internal capsule and cerebral cortex. In the lateral proprioceptive path there are of neurons of the first order degenerated fibers in the dorsal spinal root; of neurons of the second order degenerated fibers of the fasciculus anterolateralis superficialis and in the fasciculus spinocerebellaris, as well as destruction of nerve axons in the dentate nucleus. In the ventral proprioceptive conduction path there are at the levels of the neurons of the first order degenerated fibers in the fasciculus gracilis and cuneatus; of neurons of the second order hemorrhage and destruction of nerve fibers in the thalamic nucleus; of neurons of the third order hemorrhages and destruction of nerve fibers in the internal capsule and cortex. In the descending cerebrospinal pathways for voluntary muscular control there are at the level of neurons of the first order hemorrhage and destruction of nerve fibers in the motor areas of the precentral gyrus, also degenerated fibers in the fasciculus cerebrospinalis of the spinal cord; of neurons of the second order degenerated fibers in the ventral spinal roots. In the descending cerebellar pathway there are at the level of neurons of the first order destruction of nerve fibers in the dentate nucleus.

There is then in fat embolism of the central nervous system a condition that produces profound injuries to the anatomical pathways and centers which represent all types of functional connections.

To attempt to correlate the symptomatology with the observed lesions on the basis of the study of a single case is unsafe, irrespective of the completeness of the study. We can, however, point out certain relationships in which the observed lesions might have been contributory, if not the cause, of the clinical manifestations.

Delirium: Hirsch[21] defines delirium as a psychopathic condition observed in the course of numerous diseases, characterized by incoherence in the chain of conceptions and by the appearance of symptoms of psychosensory and psychomotor irritation, in which the incoherence of conceptions is evident in the disconnected and confused speech and in the aimless movements of the patient. Gowers[22] defines delirium as a condition characterized by a loss of concord of the mental processes with the actual sensory impressions of the present or the memory of those of the past; in which the mental processes cease to correspond to reality, and these may be accompanied by false sensory images without sensory impressions, or perverted sensory impressions. We shall take the liberty of assuming that the observed focal lesions of the brain initiated stimuli to the regional tissues prior to causing their destruction. Fat embolism is an acute condition, in the clinical sense of the word, but nevertheless develops gradually over a period of from twelve to seventy-two hours or longer. *Delirium invariably comes in the early part of the clinical course,* shortly after the accident, and is followed by the comatose stage three to twenty-four hours later. There is then, in most instances, a short delirious stage followed by a longer comatose stage. The delirious stage is probably initiated by the stimuli from the fat emboli, which in the smallest capillaries are separated from the nervous tissue by only a thin wall, and the distention of which by the emboli might easily cause a mechanical irritation of the nervous tissue; or possibly it is the first effect of the asphyxia that follows occlusion of the capillaries. Further, it is not unlikely that the focal hemorrhages, focal edema, and focal necrosis also produce a mechanical irritation before causing destruction of the tissue. This is compatible with the commonly accepted phenomenon that many substances which cause a final inhibition of cell activity produce an initial stimulation. Cushing[23] has demonstrated that stimulation of the postcentral gyrus in the conscious patient resulted in cutaneous sensations which were subjectively localized as if coming from the skin, and that stimulation of the precentral gyrus[24] resulted in typical motor responses.

21. Hirsch: Ref. Handb. Med. Sciences, 1901, iii, 398.
22. Gowers: Diseases of the Nervous System, 1896, ii, 104.
23. Cushing: Brain, 1909, xxxii, 44.
24. Cushing: Jour. Am. Med. Assn., 1908, L, 847.

In the three blocks of tissue examined from the somatic muscular and cutaneous sensory areas of the postcentral gyrus, taken from the regions adjacent to the motor areas of the left and right legs and the motor arm area of the left cerebral hemisphere, multiple focal lesions are found; and in the auditory area of the superior and middle temporal gyri and in the sensory visual area of the calcarine fissure the lesions are observed. It is also quite likely that they are present in every other sensory area of the brain. *These lesions caused initial stimuli of the regional tissue and probably resulted in psychosensory irritation.* In the three blocks of tissue from the somatic motor areas of the precentral gyrus multiple lesions are observed. *These probably caused initial psychomotor irritation.* In the area of motor speech coordination in the triangular part of the inferior frontal gyrus multiple lesions are observed. The lesions in this area alone might account for incoherence of speech. Further, in the frontal and parietal association areas multiple lesions are also observed, which may have caused a loss of the stereognostic sense and incoherence in the chain of conceptions; and finally, similar lesions are observed in the great coordinating center, the cerebellum. That delirium may be caused by multiple focal lesions has been noted many times. Gowers states that among the organic lesions producing delirium is multiple degeneration. Hirsch states that delirium may arise in organic diseases of the brain as a sequel to minute hemorrhages, and Smith[25] describes punctiform hemorrhages in the morbid anatomy of delirium.

Coma: This does not permit of as careful an analysis as does delirium. Most writers regard it as a symptom occurring in a large variety of diseases, and as such there has been a reluctance to describe definite pathologic changes to it. Gowers[22] defines coma as a prolonged loss of consciousness, in which the patient cannot be aroused and in which the reflexes of the limbs are decreased or lessened, accompanied by a general loss of muscular tone and by disturbance in the respiratory rate and rhythm. Mercier[26] describes coma as being associated with those cases in which there is a state of evident defect of consciousness, together with a tendency to death by asphyxia; it is accompanied by a paralysis, more or less complete, of the voluntary muscles and an incomplete paralysis of the visceral musculature; independent movements of the eyes may occur, and death may result from a failure of respiration. He regards coma as a late stage in the operation of the law of dissolution, in which the highest nervous processes, being the latest and least organized, are the first to disappear; and the lowest nervous processes, being the longest and most completely organized, are the last to disappear; this law being a reversal of the law of evolution. This analogy is very interesting from the phylogenetic point of

25. Smith, Allbutt and Rolleston: System of Medicine, 1910, viii, 899.
26. Mercier: Brain, 1886-7, ix, 467.

view and from the fact that it removes the phenomenon of coma from the phase of an accidental occurrence in disease and places it definitely in the working order of a great fundamental law; but it nevertheless does not aid in its analysis along anatomic-pathologic lines. We believe that irrespective of the cause of coma the functional alterations of the nervous system have anatomic-pathologic equivalents. Edema, hemorrhages, necrosis, among others, have been mentioned; these are present in fat embolism. We regard the wholesale injuries to the entire system of conduction pathways and the functional areas of the brain of greater significance. The violent delirium of the patient forbodes impending necrosis of the regional nervous tissue of the brain in fatally terminating cases of fat embolism; and this necrosis has been amply demonstrated throughout the central nervous system.

In attempting to prove a direct relationship between the brain changes and the clinical symptoms, it is evident that if similar lesions can be demonstrated in other diseases associated with delirium and coma, the relationship in fat embolism tends by analogy to become established. Accordingly a study was made of the literature of those diseases in which occlusion of the brain capillaries is likely to occur. This is true of all parasitic diseases in which free parasites circulate in the blood, and in certain diseases associated with embolus formation. The study has been partially successful; and while the results have not been as gratifying as was to be hoped, this is not to be taken as failure to establish the connections between the brain changes and the clinical manifestations in all these diseases, but rather to the limitations of our study.

In malaria of the so-called pernicious type an almost identical relation exists between the cerebral symptoms and brain changes. Clinically, delirium followed by coma has often been described. In Ewing's[27] study of nine cases of fatal malaria five of the patients developed delirium followed by gradually deepening coma, two went into coma without delirium, but the cause of death in these two was not shown to have been due to malaria. In one the probable cause of death was endocarditis, and in the other the diagnosis of malaria was only questionably established. The length of time that the patients lived after the appearance of these symptoms varied from a few hours to several weeks. Ewing concludes that the cerebral symptoms were due to the obstruction of the brain capillaries and the subsequent circulatory disturbances. The brains of persons dying of material coma have been described as edematous, hyperemic, discolored by pigment, and containing numerous punctate hemorrhages (Spiller[28]). Microscopically, there is a massing of infected red blood cells and malarial

27. Ewing: Jour. Exp. Med., 1901-5, vi, 119.
28. Spiller: Am. Jour. Med. Sc., 1900, cxx, 629.

parasites in the capillaries, with occlusion of the vessels; occasionally there is thrombosis followed by secondary changes in the adjacent tissue. Emge[29] describes multiple small, well-defined, circular areas of necrosis about the capillaries which are filled with masses of red cells and parasites, in the brain of an old man found comatose in the street, and later shown to be suffering from pernicious malaria. In Ewing's series parasites were found in the capillaries of the brains of three patients.

In trichinosis a similar correspondence exists. Thompson[30] made a clinical study of fifty-two cases, in which there were two deaths, one patient dying from complications of lobar pneumonia and erysipelas; but in the other patient death was due to the trichina infection. This patient died in delirium with a respiratory rate of 60, pulse 132, high fever and an eosinophilia of 14 per cent. Herrick and Janeway[31] report an outbreak in an Italian family in which the mother, after a week of mild symptoms, became delirious, with a temperature of 104, pulse 130 and a rapid respiratory rate. In trichinosis the parasites circulate freely in the blood according to Herrick and Janeway, also Packard,[32] and as such may become emboli. Frothingham[33] tells of having found them in the brain tissue. The capillaries were occluded and some were broken through by the parasites, which then made their way into the brain substance, where they incited round cell infiltration and caused local destruction of tissue and punctate hemorrhages.

Armstrong and Mullally[34] report two fatal cases of filariasis that strongly suggest the presence of parasites in the brain, but unfortunately the brains were not examined. Both patients were young girls, who soon after admittance to the hospital developed a high fever, 103 and 104, the pulse became weak and rapid, 136 and 134 respectively; the respiratory rates were 24 and 60; both became delirious, then comatose, and died without regaining consciousness. Filarial parasites in the blood have been frequently demonstrated. Connal[35] found them in the blood of 25 per cent. of seven hundred Langos natives. Our efforts to find a specific instance in the literature where they have been demonstrated in the brain have not been successful thus far; but in view of their frequent and repeated demonstration in the blood it seems probable that a thorough search might meet with success.

Cerebral embolism from valvular endocarditis is frequently reported in the literature. A single instance by Peabody[36] will be

29. Emge: Tr. Chicago Path. Soc., 1914, ix, 133.
30. Thompson: Am. Jour. Med. Sc., 1910, cxl, 157.
31. Herrick and Janeway: The Archives Int. Med., 1909, iii, 263.
32. Packard: Jour. Am. Med. Assn., 1910, lix, 1297.
33. Frothingham: Jour. Med. Research, 1906, xv, 483.
34. Armstrong and Mullally: Surg., Gynec. and Obst., 1914, xix, 699.
35. Connal: Jour. Trop. Med., 1912, xv, 5.
36. Peabody: Med. Rec., New York, 1883, xxiv, 633.

cited, because it is typical for our purpose. The patient, a young man, suffered from palpitation of the heart, dyspnea, edema of the feet, shortness of breath, fluid in the pleural cavities; the apex beat was diffuse and there was a loud systolic murmur. On Oct. 20, 1883, he became restless and had incontinence. During the two following days the restlessness increased, and on October 22 he was quite delirious, so that he had to be restrained; morphin was administered, but it failed to quiet him. On October 24 the delirium subsided, he became quiet and was removed from the straight-jacket. He soon sank into a stupor, which gradually deepened, and he died on October 25 without regaining consciousness. On postmortem examination the basilar artery was seen to be plugged with emboli. The entire lumen of the vessel was obliterated. There was edema of the brain and the ventricles were dilated. In the mitral valve both cusps were markedly thickened and quite rough. On the roughened edges could be seen many little vegetations of fibrin and fibrous connective tissue. Peabody thinks that this was the origin of the numerous emboli in the cerebral vessels, and that the cerebral symptoms were coincident with the lodgment of the emboli in the brain.

TABLE 3.—A Comparative Study of Cerebral Embolism

Disease	Delirium	Coma	Observer	Emboli and changes in the brain	Observer
Fat embolism...	+	+	Scriba	+	Scriba
Endocarditis ...	+	+	Peabody	+	Peabody
Malaria	+	+	Ewing	+	Emge
Filariasis	+	+	Armstrong and Mullally	—	
Trichinosis	+	—	Thompson	+	Frothingham

The pathology of delirium and coma has not been definitely established. From the data in the literature, there is evidence indicating that they may be caused by a variety of anatomical lesions in addition to those mentioned. Hoch[37] has studied the brain of a man dying of delirium tremens, and finds alterations in the pyramidal cells of the cortex cerebri, no mention being made of alterations of fiber tracts or evidence of focal necrosis.

CONCLUSION

In view of the profound disturbance in the central nervous system produced by the secondary changes of fat embolism, it is reasonably safe to conclude that these multiple lesions are intimately associated with the clinical manifestations of delirium and coma.

In conclusion I wish to express my deep gratitude to Drs. H. Gideon Wells, C. Judson Herrick, E. R. LeCount and R. R. Bensley for their kind assistance in this study.

37. Hoch: Am. Jour. Insan., 1897, liv, 589.

A CRITICAL CONSIDERATION OF SYSTEMIC BLASTOMYCOSIS

WITH NOTES ON CERTAIN SPECIAL FEATURES AND REPORT OF FIVE CASES *

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NEW ORLEANS

The appearance of a disease in a locality in which it had seldom or never been recognized is of somewhat more than local interest, not only from the viewpoint of geographic distribution, but also from that of causation and of variation in type or manifestation. Particularly is this true of a disease which exhibits so marked a range of appearance and so much confusion in diagnosis as does the condition generally known in this country as blastomycosis. This infection, caused by an organism or group of organisms the different strains of which are evidently related to certain of the higher molds on the one hand, and to the torulae on the other, is one of the most important of the group of mycoses.

The localized skin disease produced by this type of parasite is widely distributed geographically and is not infrequently encountered. It is fairly easy of recognition and is quite well understood, particularly from the clinical point of view. Reports of generalized invasion, however, have been relatively infrequent and from few localities. The majority of recognized cases have occurred in the Chicago district, so that for a time it was referred to by many as Chicago disease. When the wide geographic distribution and frequent occurrence of the blastomycotic dermatitis is considered, however, one gains the impression that instances of more or less generalized invasion should occur more often than is indicated by the records. This rarity of reported systemic blastomycosis would seem to depend on two factors: first, that cases of skin infection seldom develop a generalized metastatic invasion; and second, that the majority of such generalized cases show pulmonary or other lesions primarily and are usually mistaken for tuberculosis. Recent literature indicates that the disease is becoming recognized as actually having a wide distribution.

The manner in which the cases which are the basis of the present discussion were recognized is quite illustrative of the difficulty in diagnosis. They were encountered at the Charity Hospital in New Orleans

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since the reorganization of the pathological department of that institution early in 1914, under the direction of Dr. C. W. Duval. Three of the cases were from the ward services of one of us. Case 1 was considered tuberculosis until routine microscopic study of the tissues was made. Shortly afterward two other similarly mistaken cases were found by an associate (Dr. T. D. Hurley), in histologic study of necropsy material. The first of these (Case 2) had been diagnosed pellagra and pulmonary tuberculosis, the other (Case 3), as lupus vulgaris and tuberculosis of lungs and lymph nodes. Case 4 had been treated for months as surgical tuberculosis and was recognized only when a piece of excised tissue was sent to the laboratory for examination. It was then observed clinically for some time and the organism cultivated. Permission for a necropsy could not be obtained. Case 5 was diagnosed as blastomycosis, but no opportunity had been had to cultivate the organism previous to the necropsy. The heart lesion in this case is believed to be unique.

Three collections of cases have appeared in the literature, the older being those by Hektoen[1] and Montgomery and Ormsby.[2] Since then Stober[3] has added six more Chicago cases to the list. Only two of the cases included in these summaries are from European literature. That by Busse,[4] in 1894, was the first recorded systemic invasion by such a fungus, while the other was recognized shortly afterward by Curtis[5] in France. Since that time numerous other foreign reports have been made. As is also the fact in this country, many of these show confusion as to diagnosis and classification. This is true in spite of attempts to systematize the fungi, notably by Engler and Prantyl[6] Brumpt[7] and most recently in this connection by deBeurmann and Gougerot.[8] Since it is impractical and of little value to attempt to collect and classify these or the even less definite South American, Asiatic and other reports, the tabulation herein to be presented has been confined to North American cases. For consistency, therefore, we have dropped the above-mentioned first cases included by previous authors.

By a careful review we have been able to collect a total of forty-two cases which, on account of dissemination of the lesions, have, in the broad classification of American authors, been termed systemic blastomycosis. The reports so collected are shown in Table 1. For

1. Hektoen, L.: Jour. Am. Med. Assn., 1907, xlix, 1071.
2. Montgomery, F. H., and Ormsby, O. S.: Arch. Int. Med., 1908, ii, 1.
3. Stober, A. M.: The Archives Int. Med., 1914, xiii, 509.
4. Busse, O.: Centralbl. f. Bakteriol., 1914, xvi, 175.
5. Curtis, F.: Ann. de l'Inst. Pasteur, 1896, x, 449.
6. Engler and Prantyl: Natürliche Pflanzenfamilien, 1897, Part 1, Section 1 (quoted by Whitman and by MacNeal and Taylor).
7. Brumpt, E.: Précis de Parasitologie, Paris, 1910 (quoted by MacNeal and Taylor and others).
8. De Beurmann and Gougerot, Les Nouvelles Mycoses, Paris, 1911.

the sake of completeness we will add like summaries of the five cases to be described. The addition of these to the cases already on record makes a total of forty-seven American reports.

In addition to the cases listed above, there have been found several which were either too incompletely studied and reported properly to be here included, or were but indirectly referred to. For instance, Montgomery and Ormsby give details of five "probable cases." These Stober did not consider, though he did remark that he knew of seven unreported instances of similar invasion. Hutchins[9] reported briefly two cases as possibly blastomycosis. Campbell[10] speaks indefinitely of a second case from the South as reported from Texas, the first being Case 22 above. We have been unable to find the report referred to. He also states that Hutchins was now convinced that his two cases had been blastomycotic. Sheperd[11] in discussion referred to another case in Montreal, positively established at necropsy, which he had seen by the courtesy of a confrère. Breen[12] somewhat superficially describes cases of a yeast infection, referred to as saccharomycosis, which we shall discuss in another connection.

In Table 1 there is a group of reports of blastomycotic infections to which we would call particular attention, since it is our conviction that they are erroneously and unsatisfactorily classified as generalized or systemic. We refer to cases of deep-seated lesions, whether subcutaneous, muscular or of bones or joints, single or multiple, in which the lungs and other viscera escape involvement. In these the infection is confined to a part or to parts in such a manner as to be often amenable to surgical treatment in conjunction with other measures. In the table summary, Cases 2, 11, 21, 23, 24, 25 and 41 seem more or less logically classed as distinct from the typical generalized condition in which the deeper organs are involved and in which medication is usually futile. Extension, when it occurs in these cases, is either direct or by way of the lymphatic channels, and recovery usually occurs under proper treatment. The first of these, Case 2, reported by Gilchrist (Case 4 of Hektoen), was subcutaneous only and the patient recovered under local and general treatment. In Case 11, reported by Herrick, recovery followed after prolonged extensive involvement. Case 21, reported by Brewer and Wood, was a localized infection involving the vertebral column. Two operations were performed and the patient recovered. In Case 23, reported by Fowler, the breast of a married woman of 45 years was extensively involved

9. Hutchins, M. B.: Jour. Am. Med. Assn., 1898, li, 1868.
10. Campbell, J. L.: Atlanta Jour.-Rec. Med., 1909, xii, 308.
11. Sheperd, F. J., and Rhea, L. J.: Jour. Cutan. Dis., 1911, xxix, 588, and personal communication.
12. Breed, L. M.: The Archives Int. Med., 1912, x, 108.

TABLE 1.—History of Reported North—

Case No.	By Whom Reported	Where Reported	Locality	Sex	Age	Duration of Illness
1	Montgomery, F. H.	Jour. Cutan. Dis., 1901, xix, 318; Ibid., 1907, xxv, 393	Ill.	♂	33	7 mo. ulcer..... 9 mo. systemic
	Walker, J. W., and Montgomery, F. H.	Jour. Am. Med. Assn., 1902, xxxviii, 867				
2	Gilchrist, T. C.	Brit. Med. Jour., 1902, ii, 1321	Md.	♂	28	4 years.....
3	Ormsby, O. S., and Miller, H. M.	Jour. Cutan. Dis., 1903, xxi, 121; Jour Am. Med. Assn., 1903, xli, 1074	Ill.	♂	56	8 months.....
4	Cleary, J. H.	Medicine, 1904, ix, 818; Tr. Chicago Path. Soc., 1904, v, 105	Ill.	♂	23	Several months
5	Eisendrath, T. H., and Ormsby, O. S.	Jour. Am. Med. Assn., 1905, xlv, 1045	Ill.	♂	33	2½ years.....
	LeCount, E. R., and Myers, J.	Jour. Infect. Dis., 1907, iv, 187; Tr. Chicago Path. Soc., 1907, vii, 49				
6	Bassoe, P.	Jour. Infect. Dis., 1906, iii, 91	Ill.	♂	17	15 months.....
7	Irons, E. E., and Graham, E. A.	Jour. Infect. Dis., 1906, iii, 666	Ill.	♂	47	10 months.....
8	Christensen, C., and Hektoen, L.	Jour. Am. Med. Assn., 1906, xlvii, 247	Ia.	♂	28	20 months.....
9	Christensen, C., and Hektoen, L.	Jour. Am. Med. Assn., 1906, xlvii, 247	Ia.	♂	58	2 years.....
10	Coley, W. B., and Tracy, M.	Jour. Med. Research, 1907, xvi, 237	N. Y.	♂	27	10 months.....
11	Herrick, J. B.	Jour. Am. Med. Assn., 1907, xlix, 328	Ill.	♀	24	2½ years.....
12	Montgomery, F. H.	Jour. Cutan. Dis., 1907, xxv, 393	Ill.	♂	32	2 years.....
13	Ormsby, O. S.	The Archives Int. Med., 1908, ii, 1	Ind.	♂	38	2½ years.....
14	Irons, E. E.	The Archives Int. Med., 1908, ii, 1	Ill.	♂	20	1½ years.....
15	Hyde, J. N., and Montgomery, F. H.	The Archives Int. Med., 1908, ii, 1	Ill.	♂	24	8 years (?).....
16	Oswald	The Archives Int. Med., 1908, ii, 1	Ill.	♂	Adult	(?).....
17	Krost, M. A., Stober, A. M., and Moes, M. J.	Jour. Am. Med. Assn., 1908, l, 184; The Archives Int. Med., 1914, xiii, 557; partially reported, Ibid., 1908, ii, 1	Ill.	♂	42	6 months.....
18	Churchill, T., and Stober, A. M.	The Archives Int. Med., 1914, xiii, 568; partially reported, Ibid., 1908, ii, 1	Ill.	♂	39	4 months.....
19	Lewison, M., and Jackson, H.	The Archives Int. Med., 1914, xiii, 575; partially reported, Ibid., 1908, ii, 1	Ill.	♂	17	13 months.....
20	Myers, H. J., and Stober, A. M.	The Archives Int. Med., 1914, xiii, 585; partially reported, Ibid., 1908, ii, 1	Ill.	♂	Adult	9 months.....
21	Brewer, G. E.	Proc. New York Path. Soc., 1907-08, vii, 54	N. Y.	♂	20	6 months.....
	Brewer, G. E., and Wood, F. C.	Ann. Surg., 1908, xlviii, 889				
22	Fontaine, B. W., Haase, M., and Mitchell, R. H.	The Archives Int. Med., 1909, iv, 101	Tenn.	♀ (white)	27	5 months.....

* The type of organism was ordinary budding in all cases except as follows: Not determined in Nos. 12, 14, 16, 17, 24, 25, 26, 28, 30, 39, 40 and 41; spores are also possibly produced in No. 5.

—American Cases of Systemic Blastomycosis*

Necropsy	Distribution of Lesions	Remarks
Complete	Lungs, liver, spleen, kidneys, cutaneous and subcutaneous	This is Case 3 of Montgomery and Ormsby's series
.....	Multiple cutaneous and subcutaneous.....	Recovery (Case 4 of M. and O.)
Complete	Lungs, spleen, kidney, pancreas, larynx, trachea, pleura, cutaneous and subcutaneous	Case 5 of M. and O.
Complete	Lungs, kidney, adrenal, liver, cutaneous and subcutaneous	Microscopically found in myocardium and spleen (Case 6 of M. and O.
Complete	Lungs, bronchial lymph nodes, kidney, liver, cerebrum, cerebellum, vertebrae, spinal cord, bones, cutaneous, (colon ?)	Unusual form in cerebellum (Case 7 of M. and O.)
Complete	Lungs, mediastinal lymph nodes, vertebral, cutaneous and subcutaneous	Case 8 of M. and O.
Complete	Lungs, spleen, kidney, vertebrae and other bones, cutaneous and subcutaneous	Cultivated from kidney, though none in smears or sections (Case 9 of M. and O.)
None	Widespread cutaneous and subcutaneous.....	Case 10 of M. and O.
None	Cutaneous, subcutaneous and muscular.....	Skin only examined. Sputum negative. Early later tubercle bacilli without blastomyces (Case 11, M. and O.)
None	Lungs, cutaneous (rectum ?).....	Originally called coccidioidal granuloma by authors (Case 12, M. and O.)
.....	Cutaneous, bone	Recovery (Case 13, M. and O.)
Partial	Lungs, spleen, appendix, inguinal lymph nodes, peritoneum, thigh, cutaneous	Several forms observed. Very pathogenic (Case 14, M. and O.)
.....	Lungs, knee, cutaneous.....	Very ill at time of report (Case 15 of M. and O., previously unreported.)
None	Lungs, popliteal, cutaneous.....	Organism not specified (Case 16 of M. and O., previously unreported.)
.....	Lungs (?), cutaneous, thigh, knee.....	Organism not specified (Case 17 of M. and O., previously unreported.)
By Dr. A. W. Evens (Unreported)	Cutaneous, joints, vertebrae, spinal cord, "general" in organs	Organism not specified (Case 18 of M. and O., previously unreported.
Complete	Lungs, kidney, spleen, cerebrum, cerebellum, pleura, lymph nodes, prostate, bone, cutaneous and subcutaneous	Partially reported by M. and O. Fully reported by authors.
Complete	Lungs, pleura, kidney, prostate, bone, eye, cutaneous and subcutaneous	Partially reported by M. and O. Fully reported by authors.
Complete	Lung, bone, brain, lymph nodes, cutaneous and subcutaneous	Partially reported by M. and O. Fully reported by authors.
Complete	Lungs, liver, spleen, pancreas, kidney, cerebrum, cerebellum, bone, cutaneous and subcutaneous	Partially reported by M. and O. Fully reported by authors.
.....	Vertebrae, muscles, subcutaneous.....	No mycelia in cultures; operation; recovery
Extent not specified	Lungs, spleen, cutaneous.....	First case from South.

TABLE 1.—History of Reported North American—

Case No.	By Whom Reported	Where Reported	Locality	Sex	Age	Duration of Illness
23	Fowler, R. H.	Long Island Med. Jour., 1909, iii, 423	N. Y.	♀	45	
24	Fowler, R. H.	Long Island Med. Jour., 1909, iii, 423	N. Y.	♂	30	
25	Campbell, J. L.	Atlanta Jour.-Rec. Med., 1909, xii, 308	Ga.	♂	31	17 years
26	Rusk, G. Y. Rusk, G. Y., and Farnell, F. J.	Proc. New York Path. Soc., 1910-11, x, 48 Univ. California Publ. Path., 1912, ii, 47	N. Y.	♀	63	?
27	Sheperd, F. J., and Rhea, L. J.	Jour. Cutan. Dis., 1911, xxix, 588, and personal communication	Prov. Que. (Montreal)	♂	25	9 months
28	Ravogli, A.	Lancet-Clinic, 1911, cv, 489	Ohio	♂	31	4 years
29	Washburn, R. G.	Jour. Am. Med. Assn., 1911, lvi, 1095	Wis.	♂	70	14 months
30	Rusk, G. Y., and Farnell, F. J.	Univ. California Publ. Path., 1912, ii, 47	N. Y.	♂	57	2 years
31	Boughton, T. H., and Clark, S. N.	The Archives Int. Med., 1914, xiii, 594	Ill.	♂	21	14 months
32	Boughton, T. H., and Stober, A. M.	The Archives Int. Med., 1914, xiii, 599	Ill.	♂	39	?
33	Jackson, H.	The Archives Int. Med., 1914, xiii, 607	Ill.	♂	Adult	1 year
34	Bechtel, R. E., and LeCount, E. R.	The Archives Int. Med., 1914, xiii, 609	Ill.	♂	38	7 months
35	Riley, F. B., and LeCount, E. R.	Jour. Cutan. Dis., 1903, xxi, 121; Jour. Am. Med. Assn., 1903, xli, 1074	Ill.	♂	31	6 months
36	Eisenstaedt, J. S., and Boughton, T. H.	The Archives Int. Med., 1914, xiii, 617	Ill.	♂	19	10 months
37	Shaffner, P. F.	The Archives Int. Med., 1914, xiii, 621	Ill.	♂	30	
38	Hill, H. P., and Dickson, E. C.	California State Jour. Med., 1914, xii, 120	Calif.	♂	28	1 year
39	Dickson, E. C.	California State Jour. Med., 1914, xii, 120	Ill. and Calif.	♂	Adult	1 year ?
40	Powers, C. W.	Ann. Surg., 1914, lix, 815; personal communication	Colo.	♂	51	3 years
41	Hildreth, E. R., and Sutton, A. C.	Jour. Am. Med. Assn., 1914, lxiii, 2289	P. R.	?	?	?
42	LeCount, E. R.	Bull. Johns Hopkins Hosp. 1915, xxvi, 315	Ill.	♂	26	1 year ?

Authors' Cases

Case No.	Charity Hospital Series	Sex	Color	Age	Duration	Necropsy
43	1	♂	Colored	36	7 months	Complete
44	2	♂	Colored	18	10 months	Complete
45	3	♂	Colored	36	7 months	Complete
46	4	♂	White	32	2½ years	None
47	5	♂	White	61	1 year	Complete

—Cases of Systemic Blastomycosis*—(*Continued*)

Necropsy	Distribution of Lesions	Remarks
.....	Breast, rib	Organism not specified; operation; recovery
.....	Neck (multiple abscesses), conjunctiva.....	Organisms not specified; infection spreading at time of report
.....	Bones, cutaneous and subcutaneous, inguinal lymph nodes, etc.	Operations; infection spreading at time of report
Complete	Lung, brain, meninges.....	Organisms in this and Case 29 called oidium by authors
Extent not specified	Cutaneous and subcutaneous, bones, etc., lungs, spleen, liver, pleura, peritoneum, kidney, adrenal, prostate, esophagus	Discussed a second case not in his service
Extent not specified	Cutaneous and subcutaneous, tongue, tonsils, retropharynx, bone, pleura, diaphragm	Speaks of "spores" but differentiates coccidioidal granuloma
Extent not specified	Cutaneous, bones, joints, retropharynx.....	
Complete	Lung, kidneys, brain, meninges.....	As in Case 25
Limited	Lungs, bronchial lymph nodes, spleen, liver, bones, cutaneous and subcutaneous	
.....	Lungs, cutaneous and subcutaneous.....	Vaccine treated; improved and discharged after one year
.....	Lungs, cutaneous and subcutaneous.....	Discharged on request; unimproved
Complete	Lung, liver, spleen, kidney, adrenal, brain, cutaneous and subcutaneous, bone and lymph nodes	
Complete	Lung, spleen, liver, brain, prostate, peritonsillar tissues, pleura, lymph nodes, bone, epididymis, cutaneous and subcutaneous	
Complete	Lung, pleura, vertebrae, psoas abscess, bone, cutaneous and subcutaneous	
.....	Lung (?), bone, cutaneous and subcutaneous.....	Disposition of case not indicated
Complete	Lungs, larynx, kidney, testicle, epididymis, cutaneous, subcutaneous and bones	First case of true blastomycosis in California
Report indefinite	"Widespread" visceral lesions and destruction of bones	
Report indefinite	"Advanced lesions of chest, abdomen and joints"....	Necropsy performed by Dr. J. A. Wilder and reported as blastomycosis
.....	Subcutaneous, lungs (?).....	Small forms of organisms described; recovered
Complete	Lungs, lymph nodes, spleen, kidney, pancreas, pericardium (heart), peritoneum and cutaneous	Pericardial lesion described as retrogressive lymphatic blastomycosis

Authors' Cases

Distribution of Lesions	Remarks
Lung, spleen, liver, pancreas, pleura	
Cutaneous and subcutaneous lungs.....	Unusual budding in skin complicated by pellagra (?) and pulmonary tuberculosis
Lungs, liver, kidneys, lymph nodes, cutaneous and subcutaneous	
Lungs, ribs, vertebrae, spinal cord, cutaneous and subcutaneous	
Lung, heart, pericardium, liver, brain, bones, cutaneous and subcutaneous	Diagnosed cutaneous blastomycosis by Dr. H. E. Henage about eight years before death

and an underlying rib was invaded. The patient is reported as having recovered after operation. Fowler's second case (Case 24) was also still localized at the time of report, but was said to be spreading in spite of treatment. In Case 25, reported by Campbell, the infection was of seventeen years' duration and was confined to the leg. In spite of operative interference it was continuously spreading, apparently by the lymphatics. Case 41, reported by Hildreth and Sutton from Porto Rico, was primarily subcutaneous. The lungs were perhaps involved, but this was not proved. The patient recovered under medical treatment.

When, as in these cases, the blastomycotic infection is limited to an extremity or to the superficial tissues elsewhere, the condition can often be ameliorated and perhaps cured by surgical interference, aided by proper medication. We would direct attention to the much-used analogy in tuberculosis, which infection may be cutaneous, as lupus vulgaris, systemic, usually via the pulmonary tissues, or a deep-seated tuberculosis, in which the generalization of the infection may be avoided by proper measures. Therefore, in view of the limited extent of infection, the more frequent spread by way of the lymphatics, the indicated treatment and the better prognosis we would prefer to distinguish these cases and, rather than to attempt a new term, would refer to them as cases of surgical rather than of systemic or generalized blastomycosis.

Geographically, the distribution of systemic blastomycosis is wide, almost general, though the cases ascribed to localities other than Illinois are scattered. Of the forty-seven collected cases, 53 per cent. are from that focus. Briefly, the distribution is as follows: Illinois twenty-four, New York six, Louisiana five, Iowa two, Maryland, Indiana, Tennessee, Georgia, Province of Quebec, Ohio, Wisconsin, California, Colorado (?) and Porto Rico one each.

While the focusing of the condition about Chicago may be due in part to the endemic establishment there of a particularly pathogenic fungus, or to the crowded, unhygienic living conditions of large numbers of people, particularly during the winter season, it may also be partly ascribable to an unusual efficiency of the medical profession there in recognizing the condition and to the interest which they have taken in it. The sparcity of reports from other communities, on the other hand, is undoubtedly in part due to its nonrecognition. This would seem to have been true of New Orleans, where five cases have been encountered in little more than one year.

More widespread occurrence of the condition than is indicated by present reports seems probable among communities where large numbers of people live massed in inadequate quarters, particularly where dampness and filth are the rule. This is particularly to be expected,

since it is evident that no one particular species of yeast mold fungus alone can be held responsible for the disease, but that a number of related molds may produce similar lesions. Stober investigated the living conditions of a number of the Chicago cases and made a very interesting and suggestive series of observation. His study of the molds, or mildew, found in such places points quite insistently to the adaptation of such fungi to parasitic life in the animal body. It had been our hope to extend these observations along other lines.

Studies of the cultural characteristics of different strains isolated, as well as the morphology of the organisms in the tissues of different cases, indicates that similar clinical conditions may arise from infection by different, though probably related, fungi. Certain morphological variations in tissues have been discussed in a separate publication.[13] This was occasioned by the observation in a skin lesion from our Case 2 of myriads of organisms of various sizes, the majority so small as to suggest spore formation. This has been shown to be but the result of a modified, very rapid multiplication by budding. Whether this observation or the morphologic variations reported by LeCount and Myers,[14] Smith[15] and others necessarily indicates variation in type of organism may be questioned. They are probably but incidental and temporary modifications in reaction to unaccustomed biologic influences.

Careful cultural studies of the organisms usually encountered in blastomycetes have repeatedly been made and descriptions recorded. The monograph by Ricketts[16] and the articles by Hamberger,[17] Montgomery and Ormsby, Davis[18] and particularly by Stober, are very replete. Cultures of the blastomyces were recovered from two of our cases. Neither these nor several other strains recovered from purely cutaneous infections have presented any feature not already thoroughly established.

The typical so-called blastomyces in the tissue lesion does not produce mycelia and does not form ascospores, but appears and persists in the form of more or less sclerotic, yeast-cell-like bodies which multiply entirely by budding. Isolated and cultivated artificially, it appears usually to be a mold of saprophytic type, growing at room temperature rather more readily than at 37 C., and usually very luxuriantly on bread and potato. Typically, it quickly ceases to grow in toruloid form and finally produces a white cottony mycelium.

13. Wade, H. W.: Jour. Infect. Dis., 1916, xviii (in press).
14. LeCount, E. R.
15. Smith, A. J.: Univ. Pennsylvania Med. Bull., 1909-10, xxii, 362.
16. Ricketts, H. T.: Jour. Med. Research, 1901, vi, 373.
17. Hamberger, W. M.: Jour. Infec. Dis., 1907, iv, 201.
18. Davis, B. F.: Jour. Infect. Dis., 1911, viii, 190.

Cultural variations are noted in practically all published reports. Such variations may be minor or apparently marked enough to establish different types. As a result of his observations of certain cultural features in a number of strains, Ricketts advocated an arbitrary subdivision of the group which was adopted for some time. It now seems demonstrated, however, that minor cultural variations are not sufficiently typical or constant, even after prolonged study, to use as a basis for subdividing the group. Montgomery and Ormsby emphasize this when they state that all of the described forms had been observed by them, at one time or another, in the same strain. Hamburger described a strain which had for years been cultivated in the usual mycelial form, but which finally underwent an unexpected modification, after which it persisted in growing in the toruloid form. Stober shows clearly what our own experience bears out, that Ricketts' types "represent different stages in the life history of the organism." He describes as quite frequent the separation of apparently pure cultures into two strains, one of which grows as hard, compact, white mycelial colonies which produce spores. One of us has obtained a similar subculture from a bouillon growth of the organism from our Case 4.

Somewhat different, it would seem, is that organism cultivated from the case studied by Brewer[19] and by Brewer and Wood and Zinsser.[20] This organism never developed a mycelium, but persisted in growing as a torula over a considerable period of time. A possibly similar type of organism was found by Rusk and Farnell[21] in the tissues of their cases. They describe, outside of the rather thin capsular membrane, a homogeneous, viscid capsule which served to bind, by a medium which showed delicate starlike intercapsular bands or adhesions, the organisms into zooglea masses. This is apparently an unusual feature in American blastomycosis and suggests the appearance described and pictured by Verity[22] as seen in preparations of a nonmycelial blastomyces. Rusk and Farnell considered their organisms oidia, though the cultural work necessary to establish such identity was not carried out. Breed,[12] as has been said, listed fifteen cases of various sorts from which cultures of torulous organisms had been obtained. Because of the incompleteness of the reports it cannot be asserted, but it seems quite probable, that Cases 11 and 14 of her series were instances of prolonged pulmonary infection, very possibly inaugurated secondarily by a toruloid organism of low pathogenicity. Her results with the yeast culture autobacterins and in agglutination reactions

19. Brewer, G. E.: Proc. New York Path. Soc., 1907-08, vii, 54.
20. Brewer, G. E., and Wood, F. C.: Ann. Surg., 1908, xlviii, 889 (containing a report of the bacteriologic study by H. Zinsser).
21. Rusk, G. Y., and Farnell, F. J.: Univ. California Publ. Path., 1912, ii, 47.
22. Verity, R.: Lo Sperimentale, ovvero giornale critico di medicina e chirurgia, 1912, lxvi, 1.

indicate specificity. In this connection we may remark that two quite similar cases which have been observed by confrères in this city suffered pulmonary lesions evidently due to similar nonmycelium-producing organisms. One of these was rapidly fatal. The organism from this case was under observation by one of us for several months. Under no circumstance did it produce a mycelium.

It has become necessary to recognize, therefore, as most recently indicated by Wolbach,[23] two groups of these organisms aside from the *Coccidioides immitis*. This organism, though growing as a mold, never multiplies by simple budding either in the tissues or in cultures, and is considered by American authors, particularly by MacNeal and Taylor,[24] and also by Brown and Cummins,[25] as distinct from the blastomycetes. Few European authors have studied this organism, and the distinction is not always appreciated by them.

The first type in this subdivision is the true blastomyces or budding organism, the saccharomyces or torula, which does not produce mycelium in cultures. Among the cases due to such organisms were the early ones of Busse and Bushke, and of Curtis. These are of quite frequent occurrence in Europe. Here also may tentatively be placed the case of Brewer and possibly those of Breed, and according to Wolbach, those of Rusk and Farnell. If the two local cases referred to are reported they will fall into this group.

The second type is the usual American blastomyces of Gilchrist and Stokes,[26] zymonema of deBuermann and Gougerot, the causal agent of the great majority of cases tabulated herein. This organism, which has been given various specific names, multiplies in the tissues only by budding and grows culturally both by gemmation and mycelium formation. Further subdivision of this second group may ultimately be necessary as more strains are studied, but such exact identification entails much time and careful labor and is even then more or less uncertain.

In this connection attention may be called to the regrettable lack of uniformity in the nomenclature of these infections. It has repeatedly been asserted that the general term "blastomycosis" as applied to the clinical condition is inaccurate, unscientific and misleading, in that multiplication by gemmation in the lesion is but a phase in the life cycle of the majority of organisms implicated. Morphology of organisms in the lesions or exudates is without question an unsatisfactory basis of differentiation, although by this means the coccidioidal granuloma can be identified and it is agreed that

23. Wolbach, S. B.: Boston Med. and Surg. Jour., 1915, clxxii, 94.
24. MacNeal, W. J., and Taylor, R. M.: Jour. Med. Research, 1914, xxx, 261.
25. Brown, P. K., and Cummins, W. T.: The Archives Int. Med., 1915, xv, 608.
26. Gilchrist, T. C., and Stokes, W. R.: Jour. Exper. Med., 1901, iii, 53.

a satisfactory classification must finally depend on both primary morphology and cultural manifestations of the organisms. By such means the group of organisms which do not produce mycelia can be separated with comparative ease. Subclassification of this group will depend on further observations. For example, instances of infection by a chromogenic (pink) torula are on record. The term saccharomyces, sanctioned by the usage of several authorities, is applied without regard to the action of these torulae on sugars. We would agree that for these organisms it is better to reserve the term "blastomyces." For the other type, which, though budding while in the tissues, produces mycelia on culture media, some more descriptive term, even the awkward "zymonema," would strictly seem preferable. "Oidium" cannot properly be used in view of the definition of that organism. A practical alternative might be to retain blastomyces for both groups and apply secondary modifying terms, even though both groups, as knowledge of the organisms increases, may ultimately be subject to further subdivision.

In the study of blastomycotic material from deep-seated, apparently uncontaminated lesions, coincidental occurrence of bacteria of one type or another has several times been observed. This is not a secondary bacterial contamination of open surface lesions, and is sometimes too widespread to be explained except on the ground of a general secondary invasion. When this invasion occurs, it is usually late in disease, when the resistance to invasion by, and multiplication of, bacteria of low infectivity is greatly lowered. Bacteria so found have been of various types. Hektoen found a diphtheroid in one of his cases and Zinsser observed a gram-positive coccus in a case studied with Brewer and Wood. In the eleven cases in Stober's collection were two in which such bacteria were found. In the first, Churchill and Stober (Table 1, Case 18), streptococci were isolated postmortem from the blood, pleural and peritoneal fluids and pus from the knee joint. The authors considered it a terminal invasion, as it was only met with a few days before death. In the case reported by Lewis and Jackson (Table 1, Case 19), *Staphylococcus albus* and *aureus* were isolated from the blood, pleural fluid, bile and pus from the abscesses of the knee joints, and from the left inguinal and right axillary regions.

In our own series similar secondary invaders were recovered from two of the three cases in which cultural work was carried out. In one (Case 1) there appeared at necropsy a gram-positive diphtheroid among the blastomycetes in lesions of the pancreas, lung and neck, though not present in pus from subcutaneous abscesses a few weeks before death. This diphtheroid proved nonpathogenic and is believed to be one of the numerous types of diphtheroids frequently recover-

able from tissue lesions.[27] Masses indicating antemortem dispersion of similar organisms which continued to develop after death were found in sections from Case 2. In Case 4 there was a definite, widespread invasion by a similarly associated, apparently saprophytic streptococcus. Many were found in pus freshly aspirated from unbroken abscesses. In some of the lesions there was also associated a gram-positive diphtheroid quite similar to that in Case 1. These bacteria not only caused no perceptible local or general reaction in the patients, but proved quite nonpathogenic to laboratory animals in every case.

The general features of systemic blastomycosis have been discussed repeatedly and in several instances quite thoroughly. No extensive review of the condition can be undertaken here. Briefly, it is typically a subacute or chronic infectious process, usually pulmonary at the outset, but characterized sooner or later by the development of subcutaneous abscesses, few or numerous, localized or widely dispersed over the body, and often involving bony structures, joints and surrounding soft tissues. The pulmonary lesions are at times pneumonic in type, but ultimately are proliferative, suppurative and destructive, and give many of the signs and appearance of tuberculosis.

The conditions determining infection are in general those which lower the resistance of the individual, but particularly the association with conditions encouraging mold growth, such as work or residence in damp, filthy quarters. The majority of cases have occurred in previously healthy adult males, usually living in reduced circumstances. As has been noted, Stober's investigation of the previous environment and living conditions of certain of the Chicago patients and his study of molds isolated from such places is very suggestive and, we believe, indicates the most probable source of the invaders.

Repeated inhalation of such fungi with their deposit on diseased lung surfaces, as in bronchitis, pneumonia or tuberculosis, may be sufficient to establish the infection. Whether some special sensitization must be developed, as held by Duval[28] with regard to leprosy, has not been shown, but seems doubtful. Stober recounts an incident in which a tube containing an old culture of a blastomyces was accidentally broken. Both individuals present at the time developed symptoms of more or less serious irritation of the respiratory tract, but these subsided in a few days. Possibly repeated inhalation would have established the disease. Whatever the mode of invasion usually is, factors such as adaptation of the organism to the host and susceptibility or lowered resistance on the part of the host must play important rôles. It is significant that practically all strains show very low pathogenicity for the ordinary laboratory animals.

27. Harris, W. H., and Wade, H. W.: Jour. Exper. Med., 1915, xxi, 493.
28. Duval, C. W.: New Orleans Med. and Surg. Jour., 1915, lxvii, 1009.

The atrium of infection markedly influences the onset and course of the systemic disease. While it is sometimes impossible from a patient's history to determine whether the generalization of the organism occurred as a result of primary infection of the skin or of the lung, the evidence seldom points to the former mode of dissemination. Stober remarks that of the twenty-nine cases considered by him but three had been shown to develop from cutaneous lesions, and that in these such lesions had existed for from seven to twelve years. Case 5 of our series, we are informed, had been diagnosed as cutaneous blastomycosis about eight years previous to death. In Case 2, in which there was a complication of conditions, it is possible that the blastomycosis was primarily cutaneous. This cannot be asserted, however.

The onset varies in different cases. More commonly there is a history of a severe cold with cough and often expectoration of blood-streaked sputum, though in a few instances localized painful swelling of an extremity or joint as the result of secondary involvement was the first indication of the infection. These cases seem to develop by inoculation of the pulmonary tissues and are the most severe and rapidly fatal. Only rarely is the primary and principal lesion a cutaneous ulcer or subcutaneous abscess without evidence of lung involvement. It has been pointed out that in a few cases the infection, while ultimately deep seated and more or less extensive, seems not to have become systemic, but to have spread progressively by direct extension or by metastasis through the lymphatics without involving the deeper organs. The importance of distinguishing between truly systemic infections and such limited surgical lesions has already been discussed.

Once established, the course of the disease is usually subacute or chronic. Toxicity is seldom marked, even in extreme infections, so long as the infection is uncomplicated. The patient usually emaciates more or less rapidly, becomes extremely weak, and dies of exhaustion or some intercurrent event.

A most striking feature of advanced systemic blastomycosis is the wide range of organs that have been involved and the multiplicity of infection foci, not only in the same tissue, as, for instance, the bones, but also in the different tissues and organs. It has been thought of interest to arrive at an accurate conclusion regarding the frequency with which the different organs have been affected. In doing this it is necessary to consider only those cases in which complete postmortem examinations have been made and recorded. From the foregoing Table 1 it may be seen that among the forty-two cases collected from the literature, but twenty-three included sufficient data for this purpose. To these are now added the four necropsied cases of our series at the Charity Hospital, making a total of twenty-seven postmortems.

Table 2 shows the distribution of lesions in the different organs of these cases.

TABLE 2.—Distribution of Lesions in Necropsied Cases

	Collected, 23 Cases	Charity Hospital, 4 Cases	Total, 27 Cases	Per Cent. of Total
1. Lungs	22	4	26	96
2. Skin, etc.	21	3	24	89
3. Bone	15	1	16	59
4. Spleen	13	1	14	52
5. Kidneys	13	1	14	52
6. Liver	8	3	11	41
7. Lymph nodes	9	1	10	37
8. Brain, meninges, etc.	8	1	9	33
9. Pleura, etc.	7	1	8	29.5
10. Prostate	4	..	4	15
11. Retropharynx	3	..	3	11
12. Heart	2	1	3	11
13. Peritoneum	3	..	3	11
14. Pancreas	2	1	3	11
15. Adrenal	3	..	3	11
16. Muscles, without other involvement	2	1	3	11
17. Larynx	2	..	2	7.5
18. Pericardial cavity	1	1	2	7.5
19. Intestinal tract	2 (?)	..	2	7.5
20. Epididymis	2	..	2	7.5
21. Eye	1	..	1	4
22. Tongue	1	..	1	4
23. Tonsils	1	..	1	4
24. Trachea	1	..	1	4
25. Esophagus	1	..	1	4
26. Diaphragm	1	..	1	4
27. Testicle	1	..	1	4
			169	

From the list given in Table 2 the high frequency of involvement of both lungs and skin may be seen. The bones, spleen, kidney, liver and lymph nodes follow in order, the first three being affected in 50 per cent. or more of cases. It is interesting that the brain and meninges were involved in one third of this group of twenty-seven cases and the vertebral column in six, or 12.7 per cent., out of the total of forty-seven cases tabulated. Myocardial invasion is quite infrequent, and the unique lesions in the heart of our Case 5 have been reported by Hurley[29] from these laboratories.

Table 2 also demonstrates the wide range of possible organ infection in blastomycosis, and emphasizes the multiplicity of such foci.

29. Hurley, T. D.: Jour. Med. Research, 1916, xxxiv (in press).

In the twenty-seven cases there was a total of 169 organ foci, or an average invasion of 6.25 organs per case. This of course does not consider the number of foci in a single tissue, which often attain a considerable number in such tissues as the bone and skin.

Little can be added from careful study of our cases to the generally understood pathology of the disease. As may be inferred from our description of the condition of the lung in the report of our Case 1, lesions at times may be exudative in type, producing the blastomycotic pneumonia pictured by Mallory[30] but sooner or later become proliferative and destructive. In some cases miliary proliferative lesions very closely simulating tuberculosis occur from the start. Lesions of this type are also very numerous in the liver of Case 1. In other lesions the reaction may be persistently suppurative in nature. This is exemplified by the kidney lesion in Case 3. It sometimes appears as if the tendency in different cases is either toward the proliferative lesion throughout or toward the suppurative. This may depend on the strain of the fungus, the reaction of the host and the occurrence of general secondary invasion.

An interesting feature of the histopathology of blastomycosis is the great variability in the number of organisms present and in their distribution within the lesion. In the usual lesion they are found within giant cells and free among the tissue cells, though in some sections they may be found entirely within the giant cells. Occasionally, on the other hand, none can be found within giant cells, though these may be present at times in considerable numbers. In numbers the variability is still more striking. Frequently one finds large numbers of the organisms present; these may even occasionally be the predominant cell in the field. On the other hand, the organisms may be scarce and difficult to determine. Occasionally one finds a diagnosis reported as made, or at least strongly suggested, though no blastomycetes whatever are found in the lesion.

In our Case 1 the lung lesions showed the characteristic organisms sometimes in great numbers. In the spleen, on the other hand, extensive lesions were found in which but a few organisms can be detected on careful search, and these few sclerotic cells appear much degenerated. Here are extensive areas showing widespread necrosis (necrobiosis), with little leukocytic infiltration and no fixed-tissue proliferation. No tubercle bacilli were found. An apparently similar lesion is spoken of by Powers, reported by Whitman, as a coagulation necrosis, and other authors, as Montgomery, Case 12, have spoken of like conditions. The organism in Powers' case, however, has been shown by MacNeal and Taylor to have been the *Coccidiodes immitis*.

30. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia and London, 1914, p. 231.

In the liver of our case in question are very numerous miliary areas of primarily proliferative nature, with infiltration of endothelial leukocytes, and central necrosis. Here, too, very few blastomycetes can be found. Explanation of such lesions have never been entirely satisfactory. Were the organism a strong toxin-producer and capable of causing considerable areas of toxic necrosis from small or distant collections of the yeast cells, such lesions might be expected. The appearance of the usual type of lesion does not give credence to this, nor do the results of cultural study and animal inoculation. Another possibility is that these areas of mass necrosis are in effect infarcts, caused by capillary embolism. Their irregular distribution and variability in size in the spleen under consideration does not bear this out. Furthermore, the miliary lesions in the liver of this case, nontuberculous, can only be explained on the ground of local active infection.

In attempting to establish the real cause of such lesions we considered the possibility of a more or less indefinite protoplasmic form of the organism, possibly endowed with an ameboid motility, upon which the customary capsule would not, for a time, at least, develop. Such an organism might easily escape detection in lesions since the protoplasm of the blastomyces cannot be brought out differently by tissue stains, though the capsule can be differentially stained, particularly by Mallory's connective tissue stain. We have applied a considerable variety of stains to sections of the lesions described, but have obtained no definite results. In many of these sections the connective tissue stain reveals more or less homogeneous grayish to blue colloid bodies which cannot be distinguished from certain nonfuchsinophilic inclusion bodies occasionally found in other lesions. Although they may merely represent a result of cell degeneration, their unusual number in the spleen and liver lesions described make them of rather more than passing interest.

As for the treatment and prognosis of blastomycosis, nothing new can be added as a result of our experience. It still seems that the truly systemic infections are very refractory to treatment, and seldom recover. It is possible, however, that as a result of further experience this statement will be modified, as it is not unlikely that some strains of the organism will be found more amenable to treatment than others, a matter to be borne in mind. Potassium iodid in large doses is indicated, together with general dietary and hygienic measures. The localized surgical infections, on the other hand, are not infrequently curable by a combination of medication and surgical interference. A consideration of the cases in Table 1 seems to indicate, as in Case 25, for instance, that radical measures should not be too long delayed.

Vaccine therapy offers a field for further experimentation and observation. Stober cured one systemic case and concluded that the

method might be useful in diagnosis and valuable in therapeusis. Breed's results in this connection are also of interest. It must be noted, however, that systematic work, such as that with the blastomyces by Davis and with *Coccidiodes immitis* by Cooke,[31] has failed to indicate any high degree of immunologic reaction in such infections, which would make it appear doubtful whether constantly good results can be expected by attack along these lines. In but one of our cases, Case 4, was the organism recovered in pure culture in time to prepare a vaccine. The condition of the patient was then, however, too poor to warrant its use.

The five cases of systemic blastomycosis encountered in this department occurred within less than a year, between July, 1914, and January, 1915, inclusive. This, however, does not necessarily indicate the frequency of occurrence in this locality, since no case has been detected among the 450 necropsies performed since that time. The following reports are made as brief as is consistent with a clear exposition of the condition.

REPORT OF CASES

Case 1.—H. J., colored, laboring man, aged 32, single, a native of Louisiana, was admitted to the Charity Hospital, Ward 34 (service of one of us), Jan. 22, 1914, complaining of pain in the right side of chest, cough, fever and expectoration.

His history was negative. Present illness began three months before with cough and pain in the right chest, the latter recently extending to the shoulder. For two months had expectorated purulent material. Had fever late in the day and sweats at night.

On physical examination the patient was found to be a well-developed and well-nourished man. The superficial glands were palpable. Inspection showed a marked diminution of expansion on right side of the chest, slight on the left. Tactile fremitus was diminished and dulness was marked on the right side, especially in the upper part. Here was a distinctly visible pulsation which was felt on palpation. Respiratory sounds here were practically absent; voice sounds were diminished. Over this area a distinct bruit was heard, synchronous with the second sound of the heart. Respiratory and voice sounds were diminished throughout, and friction sounds were present in the right axilla.

The heart was negative except for a slight increase to the right. The liver was palpable one and one-half inches below the costal arch. The abdomen was otherwise negative.

The temperature at admission was 101, respiration 28, pulse full, feeble and regular. The blood pressure was the same in both arms, systolic 110 and diastolic 50. The blood counts showed 10,000 white and 3,900,000 red cells. Hemoglobin was 60 per cent. (Tallqvist). The Wassermann reaction proved negative, original and Tschernogubow technics. Specific gravity of urine 1.030, hyaline and granular casts. Though the sputum was repeatedly negative, the provisional diagnosis was pulmonary tuberculosis, probably with aortic aneurism. The roentgenologist reported "probable thoracic tumor."

On March 16 a small, freely movable nodule had appeared above the right clavicle. This rapidly enlarged, became fluctuant and was incised on the third or fourth day, when a small quantity of thick, yellowish pus was evacuated. The skin lesion quickly healed. On March 20 another hard nodule was noticed

31. Cooke, J. V.: Arch. Int. Med., 1915, xv, 497.

on the nose; it quickly softened, was opened and rapidly healed. The purulent material obtained was negative for *B. tuberculosis* and cultures were reported sterile.

About six weeks before death a large abscess appeared on the right leg below the knee. This rapidly attained a diameter of about eight inches when it was opened and about a pint of pus obtained. In two or three weeks the lesion was completely healed. This pus was also reported negative for bacteria, in smears and cultures.

The patient became emaciated and began to have severe paroxysms of coughing, with free expectoration of a mucopurulent material, frequently bloody. The physical signs were those of cavity formation. The clinical course was septic, the temperature remaining between 100 and 103. The heart became rapid and weak, respiration increased in frequency, and the cough, expectoration and sweats continued until the patient died, May 19, 1914.

In view of the fact that at no time had tubercle bacilli been found, the diagnosis of pulmonary tuberculosis, as given by the intern at the time of death, was believed to be incorrect.

Necropsy (A, 14, 175) was performed (W.) on May 22, 1914, seventy hours post mortem. The findings in abstract are as follows:

The body is fairly well developed but emaciated. No ulcer or subcutaneous abscess is evident, though there are small scars over the right clavicle, on the nose and below the right knee.

The peritoneal cavity shows very little fat. The mesenteric lymph nodes are enlarged. The pleural cavities are obliterated in their upper portions by firm adhesions, those on the right side being so firm as to necessitate cutting the lung from the chest wall. No free fluid or acute exudate is noted. In removing the right lung several abscesses are cut or torn into, some of which involve the chest wall. They contain a thick, semifluid material, yellowish gray in color and of a peculiar odor. On section numerous smaller cavities are found, separated by zones or walls of increased connective tissue. These walls are covered by necrotic material and purulent exudate. The lower lobe is large, heavy, dark red in color and contains numerous small, usually grayish areas of solidification. The larger show central necrosis. The left lung presents a condition essentially similar except that there is a greater amount of apparent organization with but a few small abscesses.

The organs of the neck are examined here because of apparent involvement in the condition found in the right pleural cavity. Below the thyroid and behind the upper part of the sternum and right clavicle is a small abscess. This does not communicate with the surface or directly with the cavity of the adjacent lung.

The spleen is enlarged and weighs 200 gm. On section there are found areas of an apparently granulomatous change, firmer and paler than the spleen pulp. The liver is large, pale and irregularly yellowish in color. On section numerous small grayish areas are seen, apparently of the same process as that involving the other organs. The pancreas, which is small and weighs but 60 gm., appears normal except for a small, yellowish abscess near the caudal end. This contains thick pus. The walls are firm and fibrous in consistence. The gastro-intestinal tract shows only a few small, indefinitely ulcerated areas in the lower part of the small intestine and in the colon. These are not distinctive in appearance. The left kidney weighs 200 gm., the right 185 gm. On section the parenchyma bulges. The cortex is somewhat thickened and granular, the glomeruli injected and prominent. Organs not mentioned are essentially negative.

Rush sections of the lung tissue, made at the time of necropsy and stained with methylene blue, showed lesions thought to be typical of pulmonary tuberculosis.

The anatomical diagnosis was as follows: Original pulmonary tuberculosis; miliary tuberculosis of spleen and liver (and intestine?); abscesses, cervical, pleural and pancreatic; congestion and edema of lungs; acute nephritis.

Bacteriologically, smears showed numerous gram-positive, non-acid-fast diphtheroidal bacilli in the purulent material from the neck, pancreas and lung. This organism was isolated and given the number D 15 in the diphtheroid series of Harris and Wade. No tubercle bacilli or actinomyces were found. (These smears, which were preserved, were later reexamined and all found to contain small numbers of shrunken blastomyces, none of which has been seen to show budding.)

Microscopically the essential features of the tissue removed at necropsy were as follows:

Certain sections of the lung showed areas of a granulomatous change typical of tuberculosis; lymphoid and plasma, epithelioid and giant cells and necrosis. There were also found, however, round, red staining bodies, each with a more or less wide, hyaline, unstained capsule. These were present within giant cells and lying free among other cells. In some areas they were numerous and in others difficult to find. Sections from the abscesses showed an extensive combination of granulomatous and suppurative reactions. There were areas of fibrosis adjoining others which, on the one hand, showed extensive epithelioid proliferation, and on the other hand in which polymorphonuclear infiltration was extensive and beyond which abscess formation was evident. In some of these sections the blastomycetes were found with difficulty. There were also found vast numbers of short, thick diphtheroidal bacilli.

The spleen pulp was congested. Large areas of necrosis were prominent about which were zones of epithelioid and lymphoid and plasma cells, with quite numerous giant cells. Prolonged examination revealed very few typical sclerosed yeast cells, although numerous bodies were encountered which may represent degeneration forms of these. The appearance is, as a whole, very typical of tuberculosis, though no tubercle bacilli can be found in specially stained sections. In the liver passive congestion is notable. Numerous small areas are composed largely of lymphoid and plasma cells with more or less numerous epithelioid cells in the larger areas. As in the spleen, a few degenerated blastomycetes were found on careful search. One section of pancreas studied showed the wall of the abscess noted. A number of typical blastomycetes were here seen among the cells of the lesion. Sections of the intestine showed nothing worthy of note. The areas thought to be ulcers were apparently caused by postmortem change. A section of the adrenal showed, besides marked postmortem change, two plugs or colony masses of bacteria. They were apparently of the diphtheroidal bacillus found elsewhere. There was no tissue reaction about these masses. The kidneys showed no increase of the connective tissue, but parenchymatous degeneration was marked. The lining epithelium was everywhere granular, swollen, fragmented, and at times vacuolated, as if by fluid. Small masses of bacteria were found, about which no tissue reaction is seen. No blastomycetes were found on prolonged search. The heart showed little but a fairly extensive fat vacuolation of the muscle fibers.

The corrected anatomical diagnosis was as follows: Blastomycosis of lung, spleen, liver and pancreas; blastomycotic abscesses, cervical, pulmonary and pancreatic, with secondary diphtheroid invasion; fatty myocarditis; acute perenchymatous nephritis; congestion and edema of lungs.

Case 2.—M. K., aged 18 years, single colored man, native of Louisiana, laborer, was admitted to the Charity Hospital, Ward 34 (service of one of us), July 4, 1914, complaining of cough, expectoration, weakness, diarrhea, fever and sweats.

His history was negative. His present illness began nine months ago with a suppurating focus in the right inguinal region and another over the sacrum. These had persisted. About six months ago he began to have pain in the chest and to expectorate freely. About this time diarrhea developed and there appeared a roughened discoloration of the skin. Diarrhea has persisted, the bowels moving several times daily. Blood was seen in the stools, but none in the sputum.

Physical examination showed the patient to be emaciated. The skin over the wrist, ankles, about the mouth and at the elbows was dry, rough and brownish-black in color. The backs of the hands were also roughened. A discharging sinus 5 mm. in diameter was found in the right inguinal region. The surrounding skin was much thickened and indurated. An area of ulceration was also present in the sacral region.

There was a diminution of expansion on both sides of the chest, dulness, bronchial respiration, increased voice sounds and many fine and coarse moist râles. In both axillary regions the respiratory and voice sounds were greatly diminished because of pleural thickening. The heart was normal and the abdomen apparently negative. The temperature was 99 F.

A blood examination on admission showed a total white cell count of 16,000 and the hemoglobin 60 per cent. (Tallqvist). The systolic blood pressure was 100. The urine showed albumin (amount not recorded) and hyaline and granular casts. On July 5 and again on the next day the sputum was found to contain tubercle bacilli.

The patient was transferred to the tuberculosis division. On July 20 he had a severe pulmonary hemorrhage. Cough persisted and became progressively worse, the sputum at times being blood streaked. Weakness was pronounced and diarrhea, sweats and chills were very troublesome. The temperature was never high, and was subnormal for the last two weeks of the patient's life, death occurring July 28, 1914.

A clinical diagnosis of pulmonary tuberculosis and pellagra was made.

Necropsy (A, 14, 274) was performed (H.) July 29, 1914, fourteen hours postmortem. The essential findings were as follows:

The body is fairly well developed but emaciated. The skin about the angles of the mouth, over the posterior surfaces of the hands and wrists and of the forearms for a distance of from 5 to 6 cm. at the ankles and over the inguinal regions is of a dark, brownish-black color, very dry, rough and scaling and in places somewhat indurated. In the right inguinal region are several small scars and a number of small ulcerated areas from 0.5 to 1 cm. in diameter. These lesions are irregular in outline, with undermined edges, and present a granulating base covered with a small amount of thick, yellowish exudate.

The peritoneal cavity contains little fat. The mesenteric lymph nodes are moderately enlarged and pinkish gray. The diaphragm is at the fifth rib on the right and the fifth interspace on the left. Both pleural cavities are practically obliterated by many dense fibrous adhesions. The heart weighs 190 gm. On section the musculature is brownish red, somewhat soft in consistency, but resistant to pressure. The valves are negative.

The lungs are removed with difficulty, a portion of the right upper lobe requiring to be cut away. Throughout both lungs many small areas of consolidation are felt; on section these are seen to be grayish yellow in color and surrounded by zones of connective tissue increase. Some of the larger of these show necrosis. In the upper lobe of the right lung are cavities which contain greenish yellow purulent exudate. The walls are made up of thickened connective tissue covered by necrotic material. The spleen weighs 80 gm. and shows nothing worthy of note. The liver is small and weighs 1,130 gm. Its outer surface is yellowish brown in color. On section some congestion is apparent. The vessels of the gastro-intestinal tract show some engorgement, while here and there minute petechial hemorrhages are seen. The right kidney weighs 190 gm. and the left 195 gm. On section the pulp bulges and the parenchyma is congested, the pyramids particularly so. The cortices seem diminished. The adrenals are negative, and the other organs present nothing worthy of particular note.

The anatomical diagnosis was as follows: Original pulmonary tuberculosis, pellagra; acute and chronic nephritis; chronic splenitis; passive congestion of the liver; chronic fibrous pleurisy, bilateral.

Microscopically, the observations worthy of note in this connection are as follows:

Sections of lung showed lesions with little acute infiltration but much necrosis. This seemed to be a mass, coagulation necrosis, since the outlines of the degenerated cells were frequently retained. There often seemed to be a preceding deposit of fibrin in the neighboring air sacs. About some of these lesions there was much fixed-tissue proliferation, with an infiltration of lymphoid and plasma cells, the latter being the more numerous. In other sections these smaller lesions had progressed to cavitation with secondary invasion and suppuration. In a few areas typical blastomycetes were found. These were within giant cells, endothelial phagocytes or were lying free in exudate or rarely in an uninvolved air sac. The number could not account for the extent of the lesions present. In many of these lesions, however, acid-fast bacilli could be demonstrated. There was an acute fibrinous exudate on the pleural surfaces.

The spleen showed little worthy of note. By careful search of several sections a very few partially degenerated blastomycetes were found, lying in sinuses with no evidence of local tissue reaction. The heart showed only a moderate hypertrophy. The liver showed no evidence of invasion by the blastomycetes. The atrophy of chronic passive congestion was quite marked. Sections of the kidneys showed congestion and hydropic degeneration of the parenchyma, but no evidence of blastomycosis. The other deep organs were practically negative.

In the sections of the only piece of skin which was preserved at necropsy, taken from the right inguinal region, there was found a condition which was made the subject of careful study. There was a lack of the epithelial proliferation and down growth common in cutaneous blastomycosis, but many small foci of necrosis were seen in the subcutaneous tissues. These were made up of large numbers of more or less degenerated endothelial leukocytes, of the débris from many very large giant cells of peculiar appearance, and of vast numbers of blastomycetes. Most of these parasites were so small as to be recognized with difficulty. Many could be made out definitely only by oil-lens study of specially stained sections, in which the very delicate, blue-staining capsular membranes were brought out. Budding was very active and occurs even in the smallest organisms, thus explaining the great number of minute cellules found.

The corrected anatomic diagnosis was as follows: Pulmonary tuberculosis; blastomycosis of the lungs and skin; pellagra (?); acute parenchymatous nephritis; hydropic; passive congestion of liver; chronic splenitis; hypertrophy of the heart; chronic fibrinous pleurisy, bilateral.

Case 3.—J. T., a colored laboring man, aged 36 years, native of Louisiana, was admitted to the Charity Hospital, Ward 23, July 31, 1914, complaining of abscesses on the chest wall and ankle, cough, fever and sweats.

His history was negative. Present illness began about four months before admission, when he developed a "cold" with cough and fever. A number of abscesses appeared, especially on the chest.

Examination showed that the patient had lost flesh. On his chest were five abscesses, three on the right side and two on the left. These varied in size from a marble to a pigeon's egg, were very painful and fluctuated. Examination of the chest revealed many areas of slight dulness, numerous râles, fine and coarse, dry and moist. The respiratory and voice sounds were increased. The heart and vessels showed nothing abnormal. Temperature was 100, pulse 112 and respiration 32.

Blood examination revealed 12,000 white cells, and Wassermann reaction negative by both original and Tschernogubow technics. The urine showed 1 per cent. albumin and hyaline and granular casts.

Abscesses continued to appear over various regions, namely, over the heart, left eyebrow, left side of neck and jaw. The patient continued to grow worse, with progressive emaciation, cough, free expectoration of a mucopurulent material, fever and sweats. The urine averaged 32 ounces in twenty-four

hours. The temperature seldom went above 100 and never above 101 until just before death, which occurred Oct. 16, 1914.

The clinical diagnosis was pulmonary tuberculosis, multiple tuberculous lymphadenitis, tuberculosis of the skin.

Necropsy (A, 14, 352) was performed (H.) Oct. 17, 1914, twenty-four hours post mortem. In abstract the findings were as follows:

The body is fairly well developed but emaciated. Three cutaneous ulcers are found. One, 1.5 by 3 cm., is above the left eyebrow; the second, of about the same size, is below the ramus of the left jaw; the third, 4 by 6 cm., is on the left side of the chest over the costosternal articulation of the fourth and fifth ribs. These ulcerations extend to the musculature. The edges are indurated, undermined, bluish gray in color and the floors are covered with thick, yellowish exudate. Five subcutaneous abscesses are present on the chest, three on the left and two on the right side. These average 4 cm. in diameter and contain a thick, purulent material. The peritoneal cavity is practically negative. The diaphragm is at the fifth interspace on the right and at the sixth rib on the left. The mesenteric lymph nodes are enlarged and average 1.5 cm. in the greatest diameter. They are dark, grayish yellow in color and many show areas of necrosis. The pleural cavities show many dense, fibrous adhesions to the apex and upper lobe of the lungs, and contain 150 to 200 c. cm. of a dark, amber-colored fluid. The heart is slightly increased in size, owing to the dilatation of the right side, and it weighs 265 gm. The valves and other structures are negative. Many hard nodules are felt throughout both lungs, most numerous in the apexes. These vary in size from small, shotlike areas to masses 1.5 cm. in diameter. On section they are grayish yellow in color and surrounded by a zone of congestion. The larger show central necrosis. Two small cavities are present in the right apex. The peribronchial lymph nodes are slightly enlarged and show some necrosis. The spleen weighs 110 gm. and presents nothing of importance. The liver weighs 1,570 gm. On section some engorgement of the venous channels is seen, otherwise the organ is negative. The right kidney weighs 135 gm. and the left 130 gm. Both are congested and show evidence of a considerable connective tissue increase. In the cortical portion of the right kidney, near the upper pole, are six small, yellowish-gray, nodular areas, each measuring approximately 2 mm. in diameter. These are outlined by congestion zones. The organs not discussed show nothing worthy of particular note.

The anatomical diagnosis was as follows: Original pulmonary tuberculosis; tuberculosis of kidneys; tuberculous lymphadenitis, mesenteric and bronchial; lupus vulgaris, face and chest wall; dilatation of heart; chronic pleuritis with effusion; chronic splenitis; chronic nephritis; passive congestion of the liver.

The microscopic examination showed the following features:

Sections of the lung were studded with miliary areas. Many of these were found to be largely collections of polymorphonuclear leukocytes, at times with much fibrin deposit, containing relatively few proliferated cells. They all contained greater or smaller numbers of the sclerotic cells of the blastomyces of various shapes, many of which were in giant cells. Other areas were largely or entirely proliferative. The larger of these showed central necrosis and suppuration. The blood spaces throughout were engorged and many desquamated pigment-bearing cells were seen. In areas of the spleen diffuse, partial degeneration was seen, being apparently postmortem changes. Throughout were many somewhat diffuse collections of polymorphonuclears. Many bacteria were present, in masses and diffusely scattered. No lesions of blastomycosis were found. In the liver were numerous collections of a few polymorphonuclears and scattered here and there were small, tuberclelike lesions showing, besides the infiltration, a fixed-tissue proliferation. A few of these showed small groups of blastomycetes, some within giant cells. The majority showed no distinct parasites, although peculiar, somewhat hyaline bodies, possibly unrecognized forms of these, were encountered. Here and there were collections or masses of irregular, hematoxylin-staining bacilli. In the adrenal were several postmor-

tem colonies of such bacteria. In certain sections of the kidney tissue blastomycotic lesions were found, in which a minimal amount of proliferative reaction, but much suppuration, was evident. The organisms were sometimes found free in blood spaces or in kidney tubules, without local tissue reaction. There was nothing else noteworthy except a moderate connective tissue increase. The skin lesions were quite typical of cutaneous blastomycosis. There was noted here and there an organism, usually with no local leukocytic infiltration, lying within the epidermis. Another feature was the unusual number of bizarre hyaline accumulation bodies which had developed by deposit increase of the capsules or shells of dead blastomycetes.

The corrected anatomical diagnosis was systemic blastomycosis, involving skin, lungs, liver, kidneys and lymph nodes; acute plastic and chronic fibrous pleuritis; dilatation of heart; chronic passive congestion of lungs and liver; acute infiltrative and chronic proliferative splenitis.

Case 4.—R. B., a single white man, aged 30 years, a native of Louisiana, was admitted to the Charity Hospital, Ward 68, Aug. 29, 1912, for treatment of growths ("papillomata") on hand and foot.

The history showed that his mother and sister died of pulmonary tuberculosis, but was otherwise negative. His present illness began about three months before admission, when fingers, hands and toes became painful. After several weeks an abscess appeared on one hand and this was opened. A week later another developed on the foot. Several weeks before admission an abscess of the back was opened and pus liberated. About two months ago there appeared on the lip, back of hand and on the great toe, cauliflower growths, which have enlarged, but have not suppurated.

Aside from these, the physical examination at admission was practically negative. Patient was in fairly good condition, seemed to be feeling well, and had no pain, cough or fever. Large doses of mixed antisyphilitic treatment were given for a long time. On August 30 pus was found in the urine but no albumin. The source of the pus is not recorded. On September 5 the Wassermann reaction was negative. The patient was discharged Oct. 8, 1912, showing much improvement.

After several months the patient applied, June 14, 1913, to the Louisiana Antituberculosis League for treatment. There he was examined by one of us (B.). The symptoms were subnormal temperature in the morning, rising to 99 and 99.8 F. late in the day; slight cough; expectoration in the morning; pain in the left side of the chest; "dyspepsia"; loss of weight. Examination showed lagging on the left side, diminished tactile fremitus, slight dulness, diminished respiratory and voice sounds and in places fine, moist râles. A diagnosis of tuberculosis of the upper part of the left lung and tuberculous pleurisy was made. The patient was sent to a tuberculosis camp, where he remained for four months with but moderate benefit. An abscess of the back having developed, he was advised to return to the hospital for treatment.

The patient, then aged 32, was readmitted Oct. 17, 1913, to Ward 68. Examination showed two large abscesses of the back, on the right side, thought to be tuberculous, with necrosis of several of the adjacent ribs. There was evidence of pleural and probably of pulmonary involvement.

Pus from the lesions contained bacteria identified culturally as pneumococci, but no tubercle bacilli were found. Wassermann reaction on October 18 was negative by the original and Tschernogubow technics. Mixed treatment was nevertheless ordered and continued for four months, with apparently little benefit.

October 22 resection of parts of two ribs, with thorough local curettage, was performed. On November 12 a portion of another rib was resected. On Jan. 7, 1914, the upper half of the former operation wound had healed, leaving a large sinus in the lower half leading obliquely upward to the ends of the previously resected ribs. Several of these ends were found exposed and necrotic. Under ether the old incision was opened, masses of soft granulation tissue removed

and a number of pockets curetted. Pleural involvement appeared on the next day, the patient being unable to breathe without severe pain. Sputum on January 9 still showed no tubercle bacilli. A consultant on this date reported the lungs negative so far as physical examination was then practicable.

On March 9, without anesthetic, the cavity and sinuses were injected with Beck's paste preparatory to Roentgen-ray examination. The roentgenologist reported "vertebrae negative, small masses of bismuth scattered through lung on right side, also a small amount in left side near base." On April 15 the wound was again curetted and more necrotic bone removed.

On two occasions the same dermatologist diagnosed the skin lesion of the face as "late tubercular syphilide." On Sept. 29, 1914, tissue curetted from the chest wall was first sent to the laboratory. In the sections blastomycetes were recognized. Cultures after two weeks gave white, fluffy growths. *Bacillus tuberculosis* was never found.

In November an abscess of the thigh was opened and early in December another posterior to the right knee was incised. Pulmonary involvement was now extensive. Many organisms were found in the sputum, and cough was severe and expectoration abundant. On December 11 the total white cell count was 13,700, neutrophils 74, lymphocytes 19, endothelial leukocytes 4, and eosinophils 2 per cent. Late in December the lesion of the back reached the cord, producing a myelitis. The constitutional symptoms were characteristic. The loss of weight and weakness were extreme. The pulse and respiration were both rapid and weak, and chills and sweats were very annoying, though in the last few weeks the temperature was persistently quite low. Death occurred Feb. 3, 1915.

The corrected clinical diagnosis was systemic blastomycosis involving the lungs, ribs, vertebrae, cord, back, face, thigh and knee, with secondary invasion of lesions by a nonpathogenic streptococcus.

Postmortem examination was not permitted.

Case 5.—M. N., a German, aged 61 years, was admitted to the Charity Hospital, May 14, 1914, complaining of cough, pain in chest, shortness of breath and weakness.

His history revealed that he had had pneumonia many years ago, but otherwise he has always been well. His present illness began with a slight cold early in February and since then he has had a cough, increasing in severity. He had expectorated but little and this never blood streaked. He has lost no weight. Examination showed the patient to be well developed and fairly well nourished, apparently not very sick. Slight edema of legs was noted. The heart was slightly enlarged to the right and downward. A faint systolic murmur was noted, heard best at the apex. The pulse was somewhat fast and slightly irregular. The arteries were markedly sclerotic. Percussion gave dulness over the upper lobes of the lungs. Râles were heard everywhere, most marked in the upper lobes. The abdomen was negative. The sputum was negative for tubercle bacilli. Probable diagnosis was pulmonary tuberculosis.

The patient was transferred on May 25 to a medical service, Ward 16, on account of bronchial asthma and valvular heart disease. The sputum was still negative. The urine was practically negative. The Wassermann reaction was weakly positive by the original technic and strongly positive by the Tschernogubow reaction. Blood pressure was 100 diastolic and 180 systolic. The von Pirquet tuberculin reaction was negative. Antisyphilitic treatment was not beneficial. Dyspnea increased in severity and frequency of attacks. The material expectorated was sometimes blood tinged.

Early in July sore areas were noticed in the scalp, and a small ulcer appeared on the left side of the face. The nodule under the scalp became semifluctuating. These lesions increasing, patient was transferred on July 6 to a surgical service, Ward 66, with a diagnosis of carcinoma of face and abscess of scalp. Histologic examination of tissue from the face lesion showed the condition to be very typical cutaneous blastomycosis. The bones of the skull were

found eroded on July 13, and a second abscess of the scalp soon appeared. The temperature had fluctuated between normal and 101 since admission, but on July 29 it rose to 104. The leukocyte count at this time was 24.000, with 87 per cent. polymorphonuclears. The right arm soon became painful at the elbow. On August 10 an abscess was opened and erosion of all the articular surfaces of the elbow noted. The scalp was reopened at the same time and the bone curetted. In August the patient left the hospital against advice.

On November 11 he was readmitted to Ward 71. He had lost 15 pounds in weight and was very weak. He coughed a great deal and had abundant blood-streaked sputum. The elbow sinus was still discharging.

All lesions progressed. Late in December two new abscesses appeared on the chest wall. The elbow infection extended through the forearm. The general condition continued to grow worse, the patient became septic and died Jan. 18, 1915.

The clinical diagnosis was blastomycosis.

Necropsy (A-15-25) was performed (H.) Jan. 20, 1915, forty hours post mortem. The essential findings were as follows:

The body is fairly well developed but emaciated. The lower extremities and right arm are edematous. The superficial lymph nodes are enlarged. On the left cheek is an indurated ulcer 5 cm. in diameter, having a granulating base showing yellowish, purulent exudate. There is a similar area, 2 by 4 cm. on the skin. Two abscesses are found beneath the scalp and two on the chest, one over the third right and the other over the fifth left costosternal juncture. The scalp abscesses communicate with intracranial collections of pus, while those on the chest arise from necrotic ribs. From the lower abscess a sinus continues inward through the fifth intercostal space and leads into the pericardial cavity. Discharging sinuses are present at the elbow of the right arm, where the bones are eroded, and extend by tracts between the muscles of the forearm to the hand. Here are sinuses and considerable necrosis of the bones of the wrist.

The peritoneal cavity is negative. The diaphragm is at the sixth rib on the right side and the sixth interspace on the left.

On raising the sternum a large collection of pus is encountered, which communicates externally with the lower subcutaneous abscess and internally with the pericardial cavity. This shows dense fibrous adhesions, among which are numerous pus foci. The heart is removed with difficulty on this account. The condition of this organ is so remarkable that it has been made the basis of a special communication. Briefly, it is much larger than normal and weighs 420 gm. Its surface shows several irregular, grayish-yellow necrotic areas which extend deep into the myocardium. One lesion in the wall of the right auricle extends through the muscularis and involves the endocardium. On opening the right auricle many minute grayish white nodules are seen on the inner wall. Some of these are entirely subendocardial, while others protrude into the cavity from 1 to 2 mm. Some of these show central cavities, and thus present the appearance of minute craters. The interauricular septum is pushed well into the right cavity by a large lesion in this wall. This protrusion is less marked in the left auricle. The muscularis of the left ventricle is much thickened, averaging 2.2 cm. The endocardium of this chamber is negative. The valves present nothing worthy of note.

The right pleural cavity contains 1,000 c.c. of clear amber fluid. There are many shreds of fibrin on the surfaces. Dense adhesions are also present at the apex and posteriorly. The left cavity contains 150 c.c. of fluid, and many firm adhesions. On pressure many shotlike nodules are felt throughout both lungs. Other larger areas of consolidation are noted. On section there are seen many grayish-yellow, solid areas surrounded by zones of connective tissue increase. Between these the lung tissue is red, and heavy and frothy red fluid exudes on pressure. The largest of the solid areas show necrotic centers. Three small cavities are found in the middle lobe of the right lung. The peribronchial lymph nodes are moderately enlarged.

The spleen weighs 280 gm. It is large and in the abundant, deep-red pulp are seen several small, soft, grayish-white nodules, pinhead in size and indistinctly marked off from the surrounding tissue by congestion. The liver weighs 1,480 gm. On section marked venous congestion and a slight connective tissue increase is apparent. The combined weight of the kidneys is 285 gm. Both show a diminution of the cortical substance and moderate congestion. The organs not mentioned present nothing worthy of note. The skull shows two irregular perforations at points corresponding to the scalp lesions. The smaller anterior perforation is continuous with a small epidural collection of pus. The dura here is much thickened and very adherent to the calvarium. Beneath the posterior opening the dura has been penetrated and the suppurative process has invaded the left cerebral cortex. The brain weighs 1,450 gm. The dura is adherent to it at both points of skull perforation. At the posterior lesion the cortex has been invaded to a depth of 0.7 cm. by the process and shows some necrosis. This is at the left superior parietal gyrus.

The anatomical diagnosis (original) was blastomycosis of the skin, lungs, bone, brain, spleen, pericardium and heart; acute and chronic splenitis; acute and chronic nephritis; chronic pleurisy with effusion.

Bacteriological examination showed blastomycetes in the preparations from the fresh material from the subcutaneous abscesses, the lungs and the pericardium, which were recovered culturally.

Sections of the heart showed, beside marked hypertrophy, areas of extensive blastomycotic invasion. The deeper, invading parts of the lesions appeared as small, discrete tubercles which showed an affinity for the connective tissue strata. Toward the pericardial surface, where the lesions were older, these had undergone fusion and showed much necrosis, with strands of connective tissue increase. Large numbers of blastomycetes were found in all sections and many of these were undergoing budding. There were also found in a few places peculiar homogeneous, hyaline bodies, similar to those described in another case in this series. The lung sections were studded with typical miliary blastomycotic lesions. The organisms were found in all lesions, but not in great numbers. The spleen showed little but a marked congestion and a fairly widespread polymorphonuclear leukocytic invasion, quite market in places. There could be found no evidence of blastomycotic invasion. The liver showed much passive congestion, with here and there a miliary lesion of blastomycosis. In but a few of these, however, could the typical blastomycetoid bodies be found. The kidney sections showed a fairly marked congestion and considerable irregular connective tissue increase. The parenchyma was swollen in places and showed much granular degeneration. The brain showed the meninges and the underlying cortical tissue to be involved in the process which caused the bone erosion. Here was much infiltration and necrosis and little or no proliferation reaction. No giant cells were seen within the cerebral substance, though several were present in the meningeal lesion. Sections of bone showed necrosis, leukocytic infiltration and proliferation of the fixed tissue. Numerous giant cells were seen, the most of which contained blastomycetes. The lesions of the skin and subcutaneous tissues were very typical of blastomycotic infection.

The corrected anatomical diagnosis is as follows: Systemic blastomycosis, involving lungs, pericardium and heart, liver, brain and ribs and bones of skull; blastomycosis of skin of face, with abscesses of scalp and chest wall; acute splenitis; acute parenchymatous and chronic interstitial nephritis; acute plastic and chronic fibrous pleurisy, with effusion.

It may be noted that in certain of the foregoing reports the clinical records are not as complete as is desirable. This is at times unavoidable in the overcrowded colored wards of a charity hospital, particularly when so commonplace a condition as tuberculosis is under treatment.

Several features have been noted which were unusual to generalized blastomycosis from the pathologic point of view or have been thought otherwise worthy of special note. Briefly, these are, in Case 1, the extensive lesions of the spleen and liver, apparently due to the blastomyces, in which very few yeast cells could be found. In Case 2 there was an apparent secondary invasion by the blastomyces of a pellagrin suffering from pulmonary tuberculosis. In the skin lesion very interesting minute forms were found and specially studied. In Case 5 the heart was very extensively involved, the condition being apparently unique. Widespread secondary bacterial invasion has been noted. These features have been considered in more or less detail.

In conclusion it may be said that nonrecognition of the blastomycosis still presents a minor problem in medical education, and the occurrence and clinical and pathologic features of the disease should be more generally understood. As has often been said, the usual error is to regard it as tuberculosis. It needs no argument to show the desirability of promptly recognizing these infections, not only from the viewpoint of mere accuracy of diagnosis and vital statistics, but from that of proper treatment, of prognosis and of prophylaxis. That blastomycosis may occur more frequently than has been recognized may be indicated by the present report of five cases discovered in fairly rapid succession in a community from which, so far as available records indicate, only the cutaneous type of infection had previously been reported. The necessity for use of the microscope in the establishment of the correct diagnosis cannot be too strongly emphasized.

We wish to express our thanks to Dr. C. W. Duval for suggestions, and particularly to Dr. T. D. Hurley of Kansas City, Mo., who as senior pathologic intern necropsied three of our cases, and studied the conditions with us. His removal from the city prevented his more active collaboration in the present article.

METABOLISM STUDIES BEFORE AND AFTER SPLENECTOMY IN A CASE OF PERNICIOUS ANEMIA*

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The present case is reported as a corollary to the other studies of metabolism before and after splenectomy reported from this laboratory.[1]

In one of these[2] the literature concerning metabolism in anemia, before and after splenectomy, is thoroughly reviewed. Few references to the literature therefore will be given here. In brief the results of studies of metabolism before and after splenectomy for various types of anemia and in normal animals may be summarized as follows: (1) There is little or no change in the total nitrogen metabolism or in its partition, with the exception of a decrease in the uric acid excretion after splenectomy in certain cases. (2) A decrease in the elimination of iron occurs in certain cases after splenectomy. (3) A decrease in the output of urobilin and urobilinogen is noted in certain cases after splenectomy.

This decrease in the daily elimination of uric acid, iron and urobilin after splenectomy is apparently most marked in those cases in which before splenectomy there has been conspicuous evidence of increased hemolysis, indicated by abnormally high excretion of uric acid, iron and urobilin or by a lemon yellow color of the skin.

Robertson[3] emphasizes the fact that cases which had shown a high urobilin excretion before splenectomy and in which after splenectomy the urobilin output exhibited only a transient reduction, or none at all, did not show as much improvement in other respects following the

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1. Austin, J. H., and Pearce, R. M.: The Influence of the Spleen on Iron Metabolism, Jour. Exper. Med., 1914, xx, 122. Goldschmidt, S., Pepper, O. H. P., and Pearce, R. M.: Metabolism Studies Before and After Splenectomy in Congenital Hemolytic Icterus, THE ARCHIVES INT. MED., 1915, xvi, 437. Goldschmidt, S., and Pearce, R. M.: Studies of Metabolism in the Dog Before and After Removal of the Spleen, Jour. Exper. Med., 1915, xxii, 319.

2. See paper by S. Goldschmidt, O. H. P. Pepper, and R. M. Pearce, reference given in Footnote 1.

3. Robertson, O. H.: Urobilin in the Stool in Pernicious Anemia, as Influenced by Splenectomy, Transfusion and Salvarsan, THE ARCHIVES INT. MED., 1915, xvi, 429.

operation as did those cases in which the urobilin output was permanently reduced after splenectomy. However, Lee, Vincent and Robertson[4] state that in some cases of severe anemia which showed marked symptomatic improvement for several months after splenectomy there was throughout this postoperative period a continued high excretion of urobilin. The highest degrees of hemolysis over a prolonged period are probably to be found in congenital hemolytic icterus. In the study of this condition reported from this laboratory[2] the output of uric acid showed a decrease of 47 per cent. after operation, the iron in the feces decreased 40 per cent. and the excretion of urobilin plus urobilinogen after the splenectomy was only about one-ninth that before the operation. The excretion of these substances had been extremely high before the operation.

The case here reported was studied in contrast as a case of pernicious anemia with evidence of increased hemolysis. The study was limited to the total nitrogen, the uric acid, the iron and the urobilin and urobilinogen. Three periods were studied: one before transfusion and splenectomy, one two weeks after splenectomy, and the third two weeks later. During each period the patient was on a carefully controlled Folin metabolic diet, and the period was not commenced until the patient had reached an approximate nitrogen balance. The nitrogen of the food and urine was determined by the Kjeldahl-Gunning method, the uric acid according to Folin's permanganate method, the iron by Neumann's method and the urobilin and urobilinogen according to the method of Wilbur and Addis. Only negligible amounts of urobilin or urobilinogen were at any time found in the urine.

The history and findings in the case will be given briefly. The blood examinations are tabulated in Table 1 and the metabolic results in Table 2.

Clinical Notes.—The patient, a man, aged 40, had complained for two years of weakness, dizziness, dyspnea and edema. These symptoms were steadily becoming worse. In other respects his history is unimportant. The physical examination revealed nothing noteworthy other than the signs of intense anemia, associated with a lemon yellow pallor. The liver edge was just palpable. At operation the spleen was found to be about three times its normal size, weighing 340 gm. The pathologic examination of the spleen showed chronic diffuse and follicular hyperplastic splenitis, with passive congestion and excessive pigmentation. The Wassermann was negative. On account of a constant eosinophilia repeated careful examinations were made of the stools for ova or parasites, but with negative results. The other laboratory reports are unimportant. The patient improved gradually after the splenectomy and six months later was doing fairly arduous work, apparently in perfect health.

4. Lee, R. I., Vincent, B., and Robertson, O. H.: Immediate Results of Splenectomy in Pernicious Anemia, Jour. Am. Med. Assn., 1915, lxv, 216.

TABLE 1.—Blood Examinations

Date	Hemoglobin, %	Erythrocytes	Leukocytes*	Nucleated Erythrocytes	Reticulated Erythrocytes, %	Remarks
3/28/15	26	1,150,000	4,600	Normoblasts + Megaloblasts +	....	Coagulation time, 4.5 min.
4/ 8/15	25	1,620,000	5,800	Megaloblasts +		
4/15/16	20	1,110,000	2,000	0	4	Hemolysis in NaCl: partial 0.425, complete 0.325
5/ 3/15	20	1,700,000	6,500	0	2	Left hospital for a month
6/ 5/15	28	1,300,000	4,300	Normoblasts +	1	Platelets less than 100,000
6/ 7/15	....	.....	.....	.....	....	Transfusion 900 c.c.
6/ 8/15	40	1,810,000	3,800	0		
6/12/15	....	.....	.....	.....	....	Splenectomy
6/15/15	37	1,420,000	16,600			
6/21/15	40	2,930,000	12,000	Normoblasts ++		
6/24/15	...	.....	.....	.....	....	Severe hemorrhage from throat
6/24/15	27	.....	.....	.....	....	After the hemorrhage
6/28/15	28	1,640,000	3,700	Normoblasts +		
7/ 9/15	31	1,630,000	6,300	0		
7/15/15	35	2,370,000	6,000	Normoblasts + Megaloblasts +		
7/22/15	48	2,030,000	8,100	Normoblasts +		
7/30/15	55	2,570,000	7,400	Normablasts +		
8/ 6/15	69	2,300,000	9,100	Normoblasts +	1	Howell-Jolly bodies +
8/16/15	48	3,200,000	8,200	0		
8/24/15	54	3,700,000	8,400	0		
8/29/15	70	3,580,000	9,400	0		
8/30/15	....	.....	.....	.....	....	Discharged
1/ 8/16	85	4,400,000	10,500	Normoblast, occasional	....	Count by Dr. S. L. Freeman

* The differential counts of the leukocytes always showed a slight eosinophilia, but were otherwise normal. The erythrocytes showed the changes characteristic of severe anemia; these became less marked as the anemia disappeared.

TABLE 2.—Effect of Splenectomy on Elimination of Uric Acid, Iron and Urobilin

Period	Date	Weight in Pounds	Nitrogen Intake, Gm.	Urine			Feces		Total Nitrogen Output, Gm.	Nitrogen Balance, Gm.	Urobilin and Urobilinogen
				Amount, C.c.	Total N, Gm.	Uric Acid, Mg.	Total N, Gm.	Iron, Mg.			
I	4/28/15	170¾	16.7	1,550	14.8	762	1.46	17	16.26	+0.44	4/9/15 to 4/12/15, 18,300 per day
	4/29/15	.....	17.6	1,820	16.2	824	1.46	17	17.66	—0.06	
	4/30/15	.....	16.7	1,600	13.7	728	1.46	17	15.16	+1.54	
	5/ 1/15	.....	17.2	1,680	14.5	788	1.46	17	15.96	+1.24	
	5/ 2/15	172½	16.6	2,200	16.2	852	1.46	17	17.66	—1.06	
	Average	.....	16.96	1,770	15.08	791	1.46	17	16.54	+0.42	
	6/12/15	175	Splenectomy								
II	6/24/15	.....	15.7	1,160	10.86	500	1.09	10	11.95	+3.75	6/25/15, 16,500 per day
	6/25/15	.....	16.8	1,340	12.48	520	1.09	10	13.57	+3.23	6/28/15 to 7/2/15, 16,000 per day
	6/26/15	.....	17	1,600	14.76	740	1.09	10	15.85	+1.15	
	6/27/15	.....	17.3	1,590	15.54	680	1.09	10	16.63	+0.67	
	Average	.....	16.7	1,420	13.41	610	1.09	10	14.50	+2.20	
III	7/ 6/15	160½	17.2	1,600	14.2	680	1.97	..	16.17	+1.03	
	7/ 7/15	.....	16.3	1,380	14.1	680	1.97	..	16.07	+0.23	
	7/ 8/15	.....	16.6	.....	.....	...	1.97	..	.....	.....	
	7/ 9/15	.....	17.2	1,210	13.44	500	1.97	..	15.41	+1.79	
	7/10/15	.....	16.8	1,310	15.06	620	1.97	..	17.03	—0.23	
	7/11/15	162	16.4	1,200	14.82	640	1.97	..	16.79	—0.39	
	Average	.....	16.75	1,360	14.32	624	1.97	..	16.29	+0.46	
	8/22/15	190	.....	.....	.....	...	....	..	.....	.....	8/18/15 to 8/22/15, 2,300 per day

COMMENT

The figures of this study as given in the Tables show that but little change in the elimination of uric acid and iron took place as a result of the splenectomy. The direction of the changes is, however, in each instance, in accord with the more pronounced changes reported where the hemolytic factor was more marked.

In view of the fact that the nitrogen balance is practically identical in the first and third periods, it may be concluded that splenectomy in this case, as in other cases reported in the literature, is without effect on the total nitrogen balance. The distinct positive balance during the second period is of interest, but probably of no significance in relation to splenic function. The uric acid elimination before operation can not be said to be other than a high normal figure, and the lower postoperative figures are still within normal range; but when it is considered that the diet and régime in general was identical before and after operation, the lowered output after operation is definite and significant. The same can be said of the figures for the iron elimination.

In the combined urobilin and urobilinogen elimination a definite change is noted following the splenectomy. Two weeks after splenectomy the diminution in the urobilin output was negligible, the difference between 18,300 units per day and 16,000 being too slight to permit of significance being attached to it. Two months after splenectomy, however, at a time when the blood count showed a pronounced and most satisfactory improvement, the urobilin output had fallen to one seventh of its former figure and had reached a low normal elimination.

SUMMARY

In an adult with pernicious anemia of a moderately hemolytic type, splenectomy was followed by disappearance of the discoloration of the skin and by prompt and persistent improvement in the condition of the blood and general health. Metabolism studies before and after splenectomy gave the following results.

1. A slight positive nitrogen balance before splenectomy was followed by an increased nitrogen retention fourteen days after operation and a return to the preoperative balance after one month.

2. The output of uric acid, although never exceeding normal limits, showed a decrease of 22 per cent. after operation.

3. The output of iron through the feces, although never above normal, showed a decrease of 40 per cent. after operation.

4. The excretion of urobilinogen and urobilin in the feces before splenectomy was about three times the normal; two months after operation the output was about one seventh of that before splenectomy.

BOOK REVIEW

MODERN MEDICINE. ITS THEORY AND PRACTICE. IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS. Edited by SIR WILLIAM OSLER, BART., M.D., F.R.S., Regius Professor of Medicine in Oxford University, England; formerly Professor of Medicine in Johns Hopkins University, Baltimore; in the University of Pennsylvania, Philadelphia, and in McGill University, Montreal; and THOMAS MCCRAE, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia; Fellow of the Royal College of Physicians, London; formerly Associate Professor of Medicine in Johns Hopkins University, Baltimore. In five octavo volumes of about 1,000 pages each. Volume IV. Diseases of the Circulatory System; Diseases of the Blood; Diseases of the Lymphatic System; Diseases of the Ductless Glands; Vasomotor and Trophic Disorders. *Just ready.* Price per volume, cloth, $5, net; half morocco, $7, net. Lea & Febiger, Publishers, Philadelphia and New York, 1915.

Volume 4 of Osler and McCrae's Modern Medicine deals with the diseases of the circulatory system, of the blood, of the lymphatic system and spleen, of the ductless glands, and with vasomotor and trophic disorders. It covers what is included in Volume 4, and in part of Volume 6 of the first edition. The general changes in typography, etc., have already been mentioned in the review of the first two volumes of the new System, in Volume XIV, page 608, of this journal.

Most of the chapters have been shortened to some extent, chiefly by the omission of the historical paragraphs, by the omission of discussions of the older theories as to the etiology and pathogenesis of various diseases, which as a result of recent advances in knowledge are now of historical interest only, and frequently by the omission or abbreviation of illustrative case reports. Many minor changes have been made, but in their general plan the articles are essentially the same as in the first edition.

A notable addition is an excellent chapter by Lewis on the Rate and Mechanism of the Heart Beat. The article by Abbot on Congenital Heart Disease has been enlarged and rewritten. The various subjects have been revised and brought up to date. This is especially true of the sections dealing with hemophilia and purpura; with the physiology and pathology of the adrenals, pituitary, and thyroid; with tetany; with the pathology of Hodgkin's disease, and with splenic anemia. Among minor additions may be mentioned short sections on *Streptococcus viridans,* endocarditis, on thrombo-angeitis obliterans, on Gaucher's splenomegaly, and on hypopituitarism.

The new edition has lost nothing essential in the revision, and is an improvement over the old in its greater conciseness and compactness, as well as in its lessened cost.

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